(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 March 2005 (03.03.2005)

PCT

(10) International Publication Number
WO 2005/018551 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number:
PCT/US2004/026065

(22) International Filing Date: 12 August 2004 (12.08.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/494,605	12 August 2003 (12.08.2003)	US
60/494,608	12 August 2003 (12.08.2003)	US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OXIME SUBSTITUTED IMIDAZO-CONTAINING COMPOUNDS

(57) Abstract: Imidazo-containing compounds (e.g., imidazoquinolines, imidazonaphthyridines, and imidazopyridines) with an oxime substituent at the 1-position, pharmaceutical compositions containing the compounds, intermediates, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

WO 2005/018551 A2

OXIME SUBSTITUTED IMIDAZO-CONTAINING COMPOUNDS

RELATED APPLICATIONS

The present invention claims priority to U.S. Provisional Application Serial No. 60/494608, filed August 12, 2003, and U.S. Provisional Application Serial No. 60/494605, filed August 12, 2003, both of which are incorporated herein by reference.

BACKGROUND

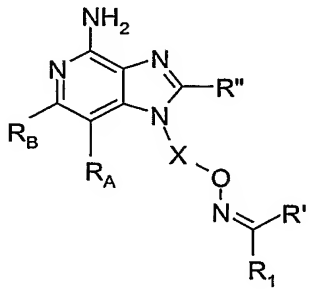
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*] pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders.

There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

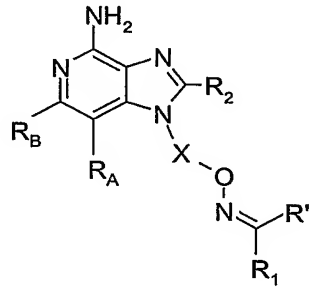
SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula I:



I

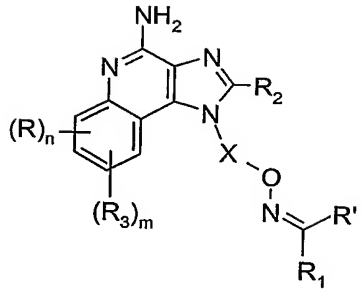
and, more specifically of the following Formula II:



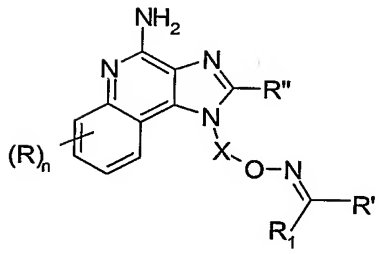
II

wherein: X, R_A, R_B, R_1, R_2, R', and R" are as defined below.

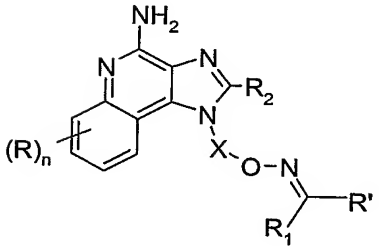
Examples of such compounds include imidazoquinolines of the following Formulas III, IV, and V, and imidazotetrahydroquinolines of Formula VII:



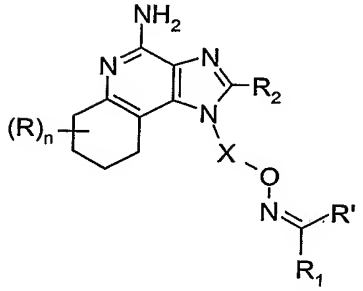
III



IV



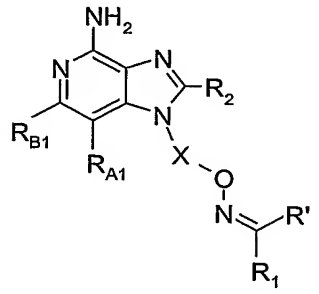
V



VII

wherein: X, R, R', R", n, m, R_1, R_2, and R_3 are as defined below.

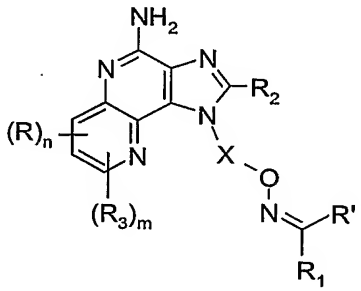
Examples of such compounds also include imidazopyridines of the following Formula VI:



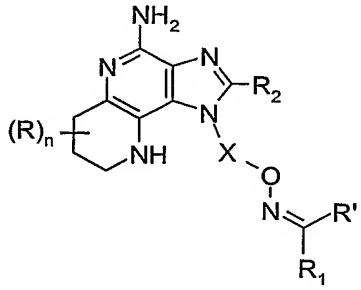
VI

wherein: X, R', R_1, R_2, R_{A1}, and R_{B1} are as defined below.

Examples of such compounds also include imidazonaphthyridines of the following Formula VIII and imidazotetrahydronaphthyridines of the following Formula IX:



VIII



IX

wherein: X, n, m, R, R', R_1, R_2, and R_3 are as defined below.

The compounds of Formula I are useful as immune response modifiers due to their ability to induce cytokine biosynthesis (e.g., induces the synthesis of at least one cytokine) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

The invention further provides pharmaceutical compositions containing an effective amount of a compound of Formula I and methods of inducing cytokine biosynthesis in an animal, treating a viral infection and/or treating a neoplastic disease in an animal by administering an effective amount of a compound of Formula I to the animal.

In addition, methods of synthesizing compounds of Formula I and intermediates useful in the synthesis of these compounds are provided.

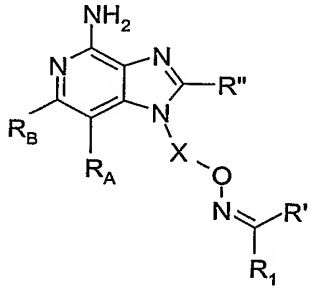
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprises" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

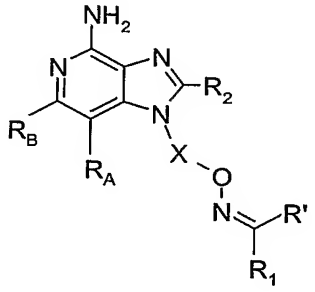
The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. In several places throughout the description, guidance is provided through lists of examples, which examples can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formulas I through IX:



I



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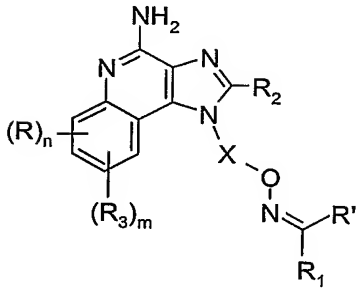

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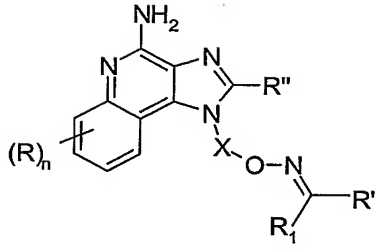
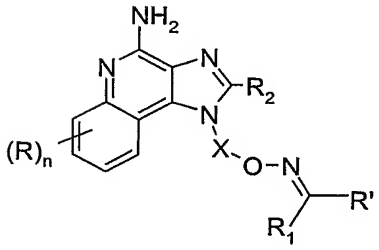
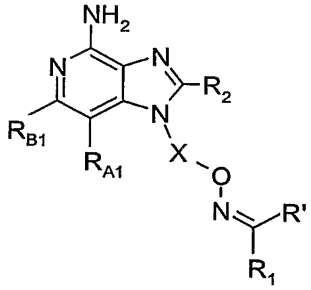


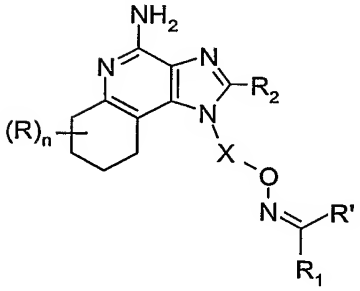
IV



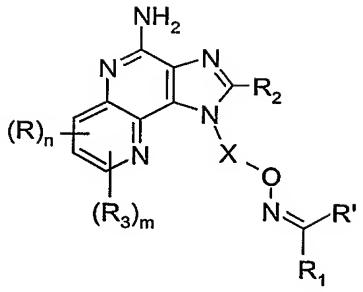
V



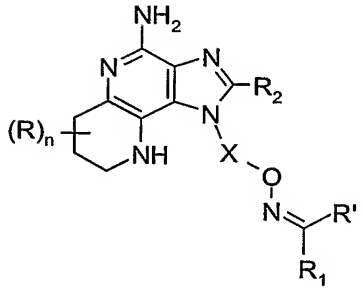
VI



VII

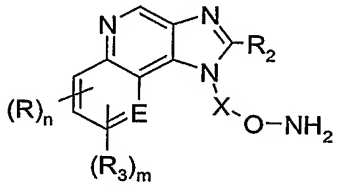


VIII

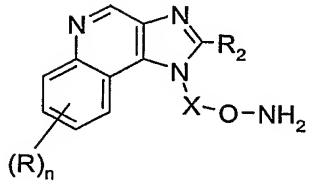


IX

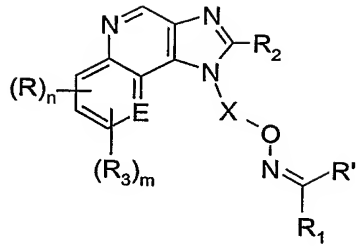
as well as intermediates of the following Formulas X through XVIII:



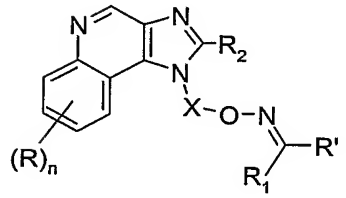
X



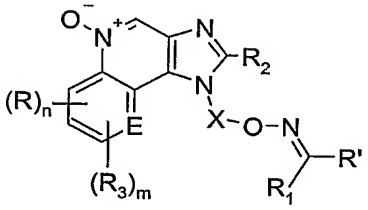
XI



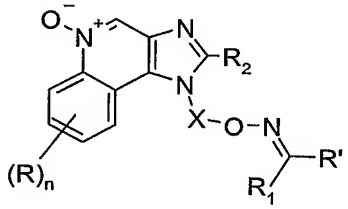
XII



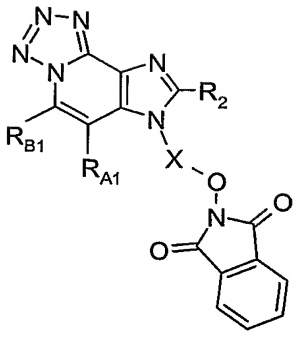
XIII



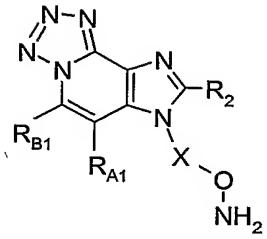
XIV



XV



XVI



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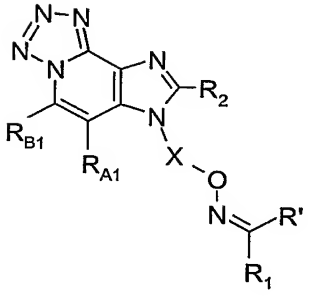
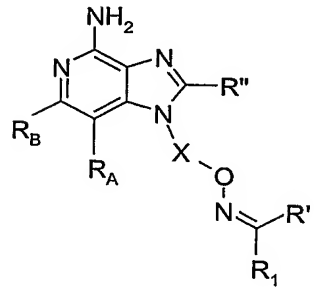


XVIII

wherein: E, X, R, R', R", n, m, R_1, R_2, R_3, R_A, R_B, R_{A1}, and R_{B1} are as defined below.

In one embodiment, the present invention provides a compound of Formula I:



I

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

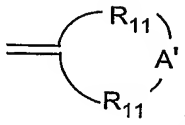
haloalkyl,

hydroxyalkyl,

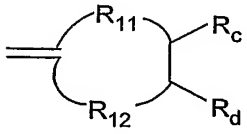
alkoxy,

dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxyl,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_6 is independently selected from the group consisting of =O and =S;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

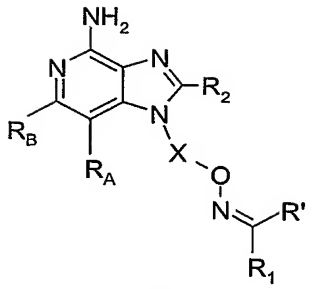
R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R" is hydrogen or a non-interfering substituent; and

each R"' is a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula II:



II

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

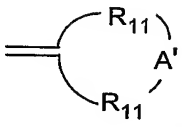
hydroxyalkyl,

alkoxy,

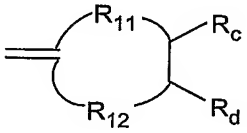
dialkylamino,

-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-$N(R_8)_2$,
-$N(R_8)$-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,
halogen,

alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxyl,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,
$-X'-R_4$,
$-X'-Y-R_4$, and
$-X'-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,
$-Z-X'-R_4$,
$-Z-X'-Y-R_4$, and

-Z-X'-R_5;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

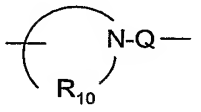
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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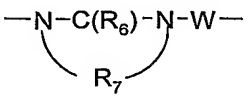

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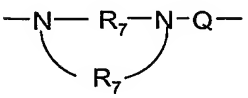

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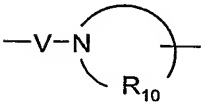

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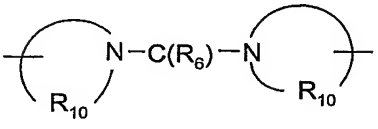
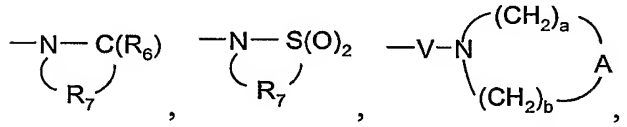


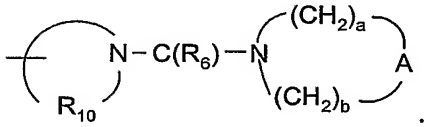
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:



and  ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

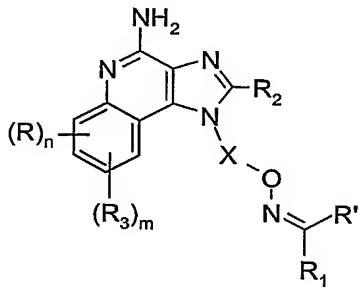
each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula III:



III

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

$-C(O)-O$-alkyl,

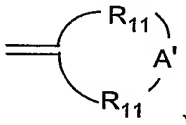
$-C(O)-N(R_8)_2$,

$-N(R_8)-C(O)$-alkyl,

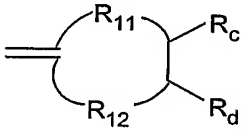
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$, and

$-Z-X'-R_5$;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

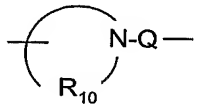
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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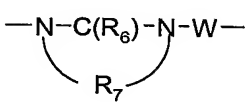

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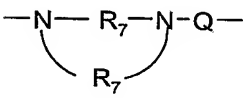

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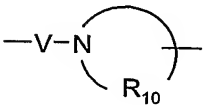

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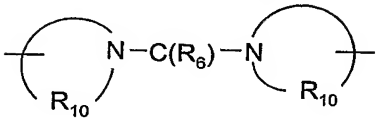


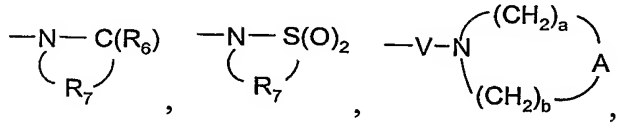
;

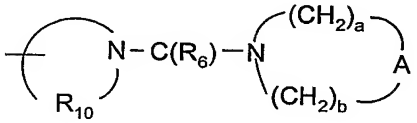
Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino,

dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:





and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and

$-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

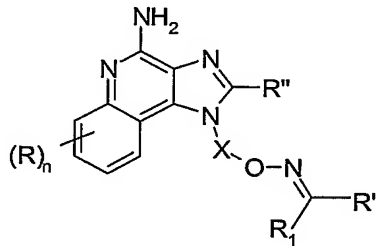
a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

n is an integer from 0 to 4; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula IV:



IV

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,
alkylene-aryl,
heteroaryl,
heterocyclyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
-O-alkyl,
-S-alkyl,
-O-haloalkyl,
halogen,
nitrile,
aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

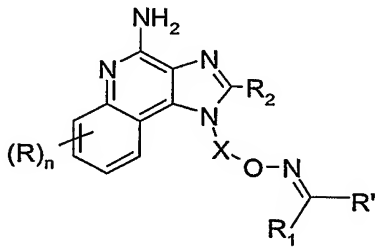
n is an integer from 0 to 4;

each R and R" are independently selected from the group consisting of hydrogen and non-interfering substituents;

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl;
or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula V:



V

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

alkylene-aryl,

heteroaryl,

heterocyclyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

-O-alkyl,
-S-alkyl,
-O-haloalkyl,
halogen,
nitrile,
aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is an integer from 0 to 4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

R_2 is selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

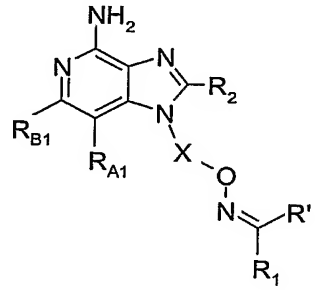
Y" is –O– or $-S(O)_{0-2}-$;

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula VI:



VI

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

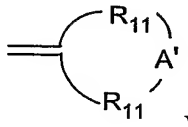
aryl,

heteroaryl,

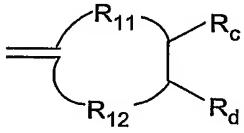
heterocyclyl,

aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

-R_4,
-X'-R_4,
-X'-Y-R_4, and
-X'-R_5;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

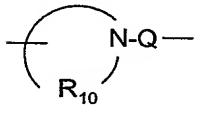
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

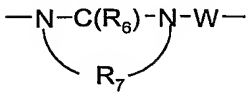
$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



,



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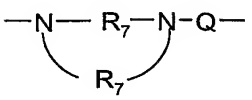

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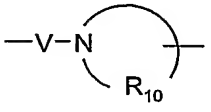
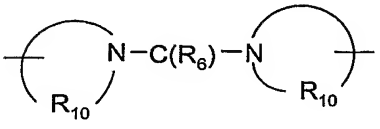


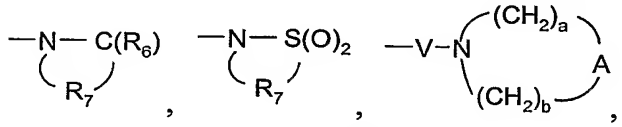
, and

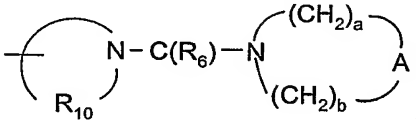


;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



and  ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or

R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

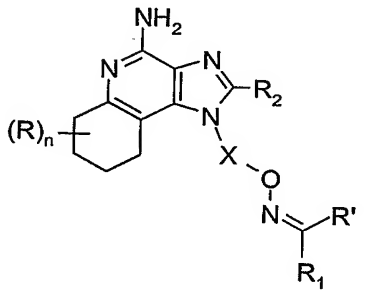
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula VII:



VII

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

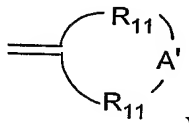
$-C(O)-N(R_8)_2$,

$-N(R_8)$-C(O)-alkyl,

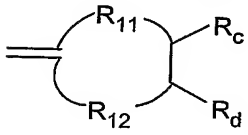
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

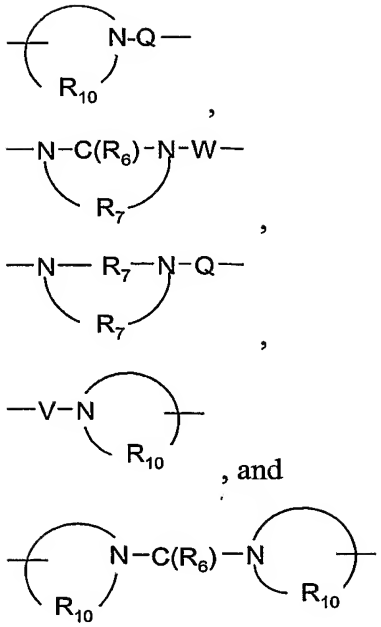
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

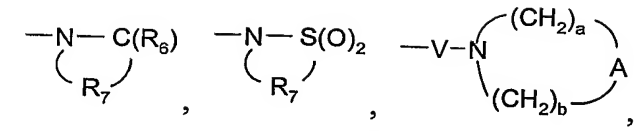
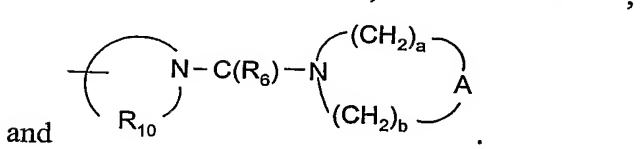
$-C(R_6)-N(OR_9)-$,



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and

$-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

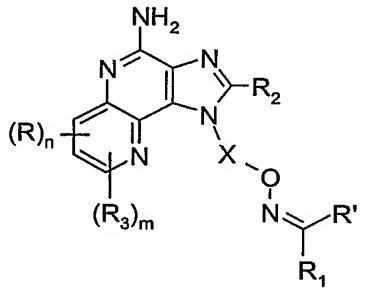
each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula VIII:



VIII

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

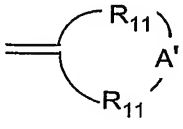
nitrile,

nitro,

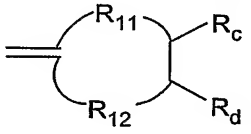
aryl,

heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:
-R_4,
-X'-R_4,
-X'-Y-R_4, and
-X'-R_5;

R_3 is selected from the group consisting of:
-Z-R_4,
-Z-X'-R_4,
-Z-X'-Y-R_4, and
-Z-X'-R_5;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the

alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

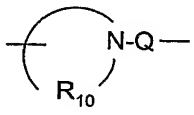
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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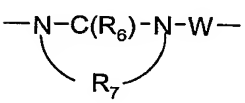

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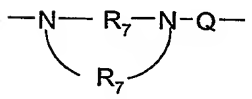

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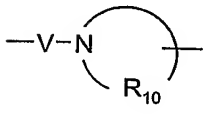

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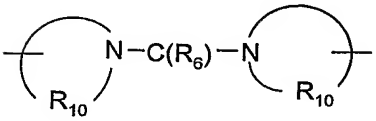


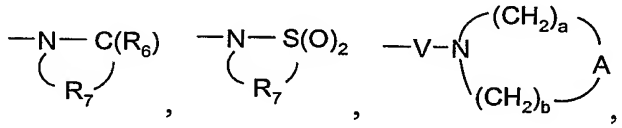
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl,

heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:



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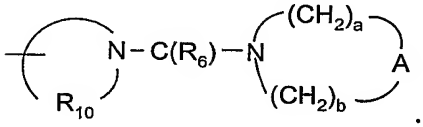


and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

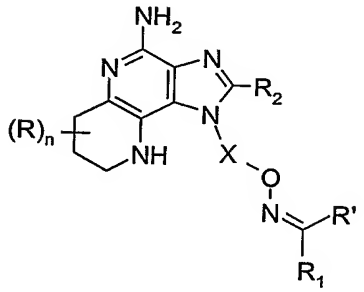
a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

n is an integer from 0 to 3; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula IX:



IX

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,
hydroxyl,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

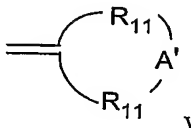
$-C(O)-N(R_8)_2$,

$-N(R_8)$-C(O)-alkyl,

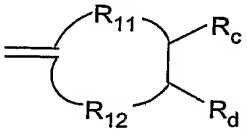
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

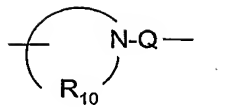
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,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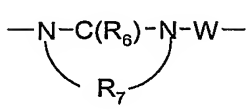
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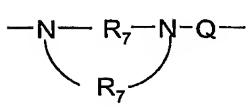
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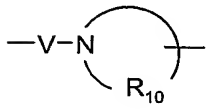
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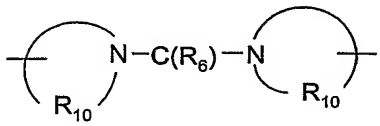
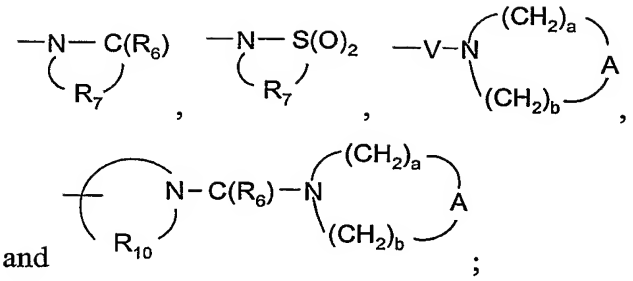

;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and

$-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

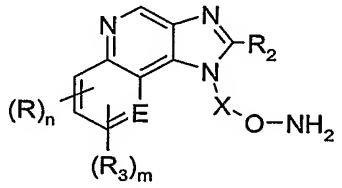
each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; and

n is an integer from 0 to 3;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula X:



X

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and n is 0 or 1, and with the further proviso that when E is CR and m is 1, n is 0;

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

n is an integer from 0 to 3;

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

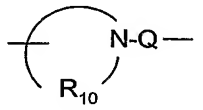
R_2 is selected from the group consisting of:
$-R_4$,
$-X'-R_4$,
$-X'-Y-R_4$, and
$-X'-R_5$;

R_3 is selected from the group consisting of:
$-Z-R_4$,
$-Z-X'-R_4$,
$-Z-X'-Y-R_4$, and
$-Z-X'-R_5$;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
$-O-C(O)-O-$,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,
$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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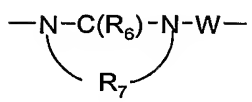

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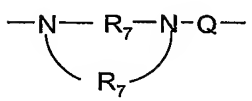

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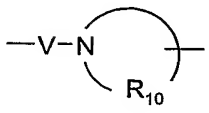

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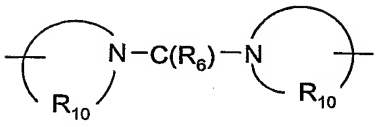
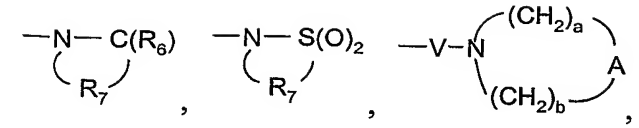
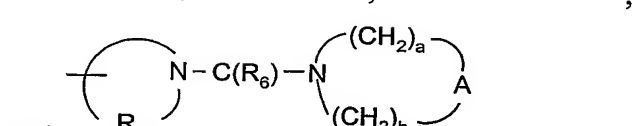


;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:



and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

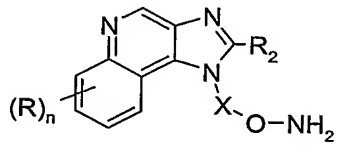
each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XI:



XI

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

n is an integer from 0 to 4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y"-alkyl,

alkylene-Y"-alkenyl,

alkylene-Y"-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

halogen,

$-N(R_{8a})_2$,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

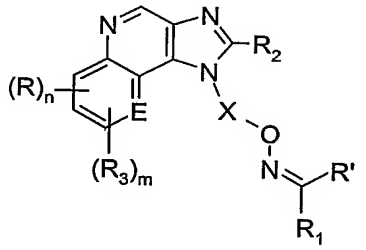
Y" is –O– or $–S(O)_{0-2}$-;

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl; and

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XII:



XII

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and n is 0 or 1, and with the further proviso that when E is CR and m is 1, n is 0;

X is selected from the group consisting of $–CH(R_{9a})$-alkylene- and $–CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

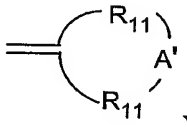
each R is independently selected from the group consisting of:

halogen,
hydroxyl,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

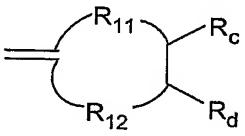
R_1 and R' are independently selected from the group consisting of:
hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,

-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

-R_4,
-X'-R_4,
-X'-Y-R_4, and
-X'-R_5;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4, and

-Z-X'-R_5;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

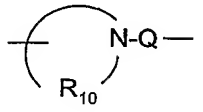
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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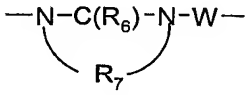

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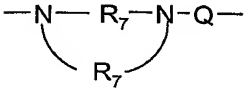

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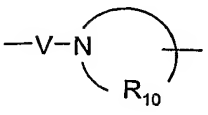
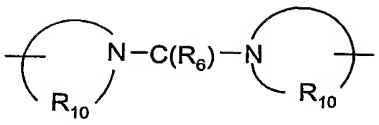


, and

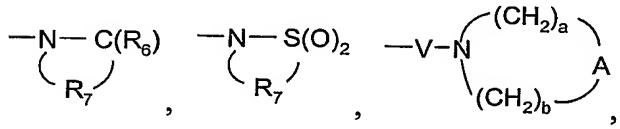


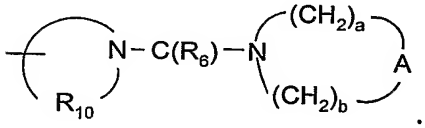
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:





and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

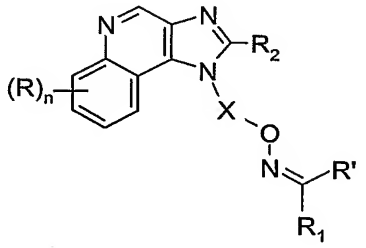
a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

n is an integer from 0 to 3; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XIII:



XIII

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

n is an integer from 0 to 4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

alkylene-aryl,

heteroaryl,

heterocyclyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

-O-alkyl,

-S-alkyl,
-O-haloalkyl,
halogen,
nitrile,
aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

R_2 is selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,
halogen,
-N(R_{8a})$_2$,
-C(O)-C_{1-10} alkyl,

-C(O)-O-C_{1-10} alkyl,
-N_3,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

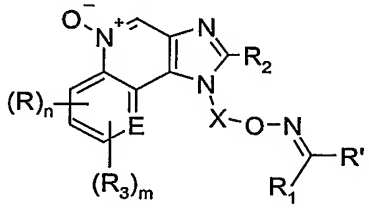
Y" is –O– or –$S(O)_{0-2}$-;

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl; and

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XIV:



XIV

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and n is 0 or 1, and with the further proviso that when E is CR and m is 1, n is 0;

X is selected from the group consisting of –$CH(R_{9a})$-alkylene- and –$CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,
hydroxyl,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

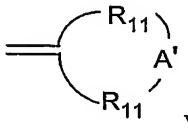
R_1 and R' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

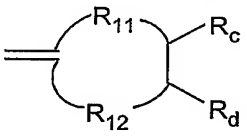
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,

-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

-R_4,
-X'-R_4,
-X'-Y-R_4, and
-X'-R_5;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4, and

-Z-X'-R_5;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

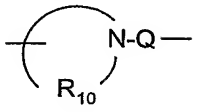
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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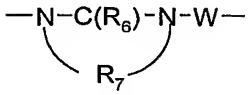

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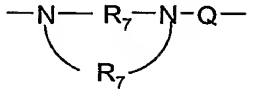

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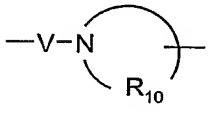
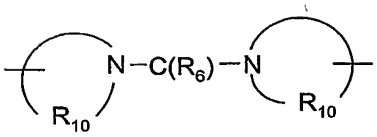


, and

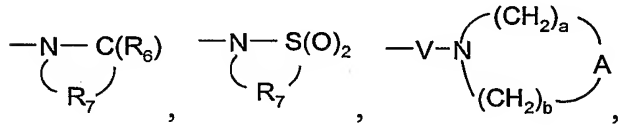


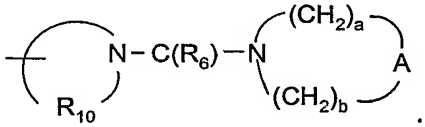
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:



and 

;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

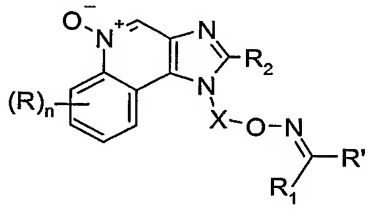
a and b are independently integers from 1 to 6 with the proviso that $a + b$ is ≤ 7;

n is an integer from 0 to 3; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XV:



XV

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

n is an integer from 0 to 4;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

alkylene-aryl,

heteroaryl,

heterocyclyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

-O-alkyl,

-S-alkyl,

-O-haloalkyl,
halogen,
nitrile,
aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

R_2 is selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,
halogen,
-N(R_{8a})$_2$,
-C(O)-C_{1-10} alkyl,
-C(O)-O-C_{1-10} alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

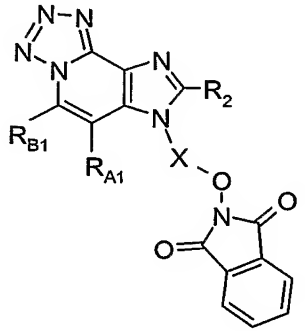
Y" is –O– or $–S(O)_{0-2}$-;

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XVI:



XVI

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

-X'-Y-R_4, and

-X'-R_5;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-$N(R_9)_2$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

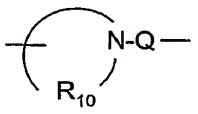
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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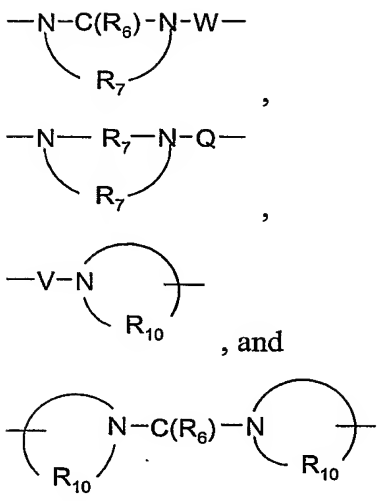
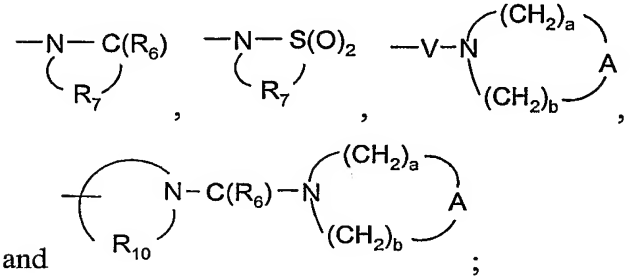


R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

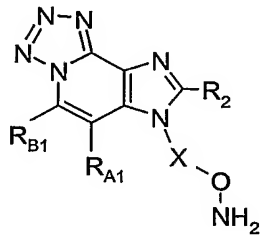
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XVII:



XVII

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

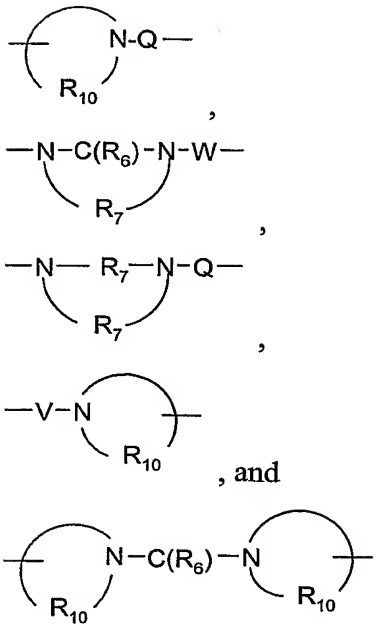
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,

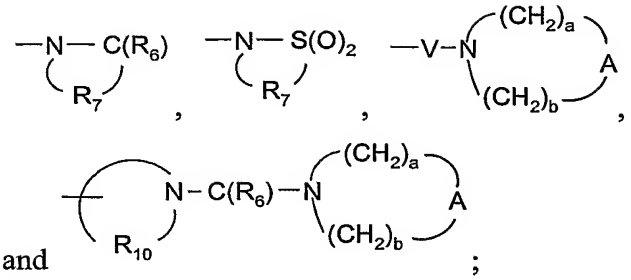


, and

;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

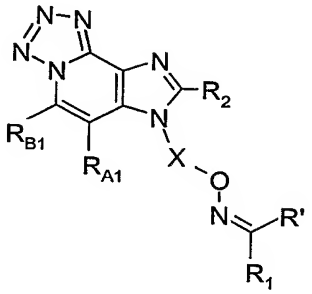
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7; or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a compound of Formula XVIII:



XVIII

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

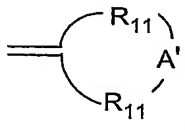
hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,

heterocyclylalkylenyl, and

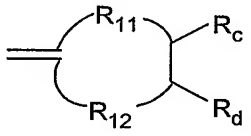
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-$N(R_8)_2$,
-$N(R_8)$-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

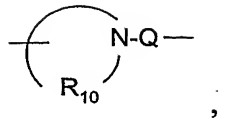
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,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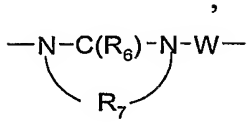
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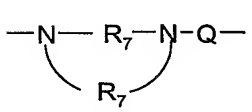
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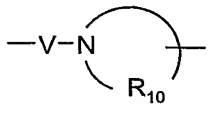
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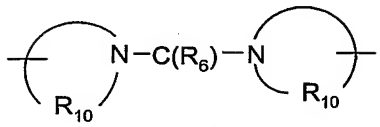
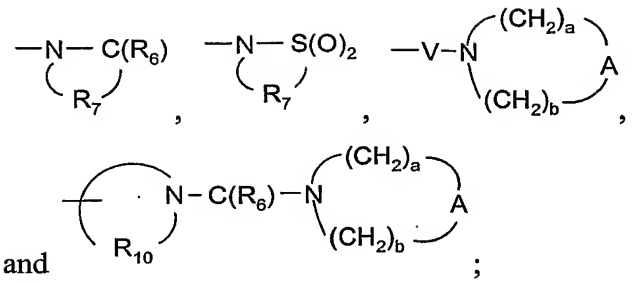

;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and

$-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$; or a pharmaceutically acceptable salt thereof.

For any of the compounds presented herein, each one of the following variables (e.g., R, R', R", R'", R_1, R_2, R_3, m, n, A, and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

For certain embodiments, each of R, R", and R'" is independently a non-interfering substituent. For certain embodiments, each R and R" is independently selected from the group consisting of hydrogen and non-interfering substituents. Herein, "non-interfering" means that the immunomodulator activity of the compound is not destroyed.

For certain embodiments, each R is independently selected from the group consisting of: halogen, hydroxyl, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain embodiments, each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl.

For certain embodiments, R_1 and R' are independently selected from the group consisting of: hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, and alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of: hydroxyl, alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, $-S(O)_{0-2}$-alkyl, $-S(O)_{0-2}$-aryl, $-NH-S(O)_2$-alkyl, $-NH-S(O)_2$-aryl, haloalkoxy, halogen, nitrile, nitro, aryl, heteroaryl, heterocyclyl, aryloxy,

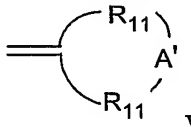
arylalkyleneoxy, -C(O)-O-alkyl, -C(O)-N(R_8)$_2$, -N(R_8)-C(O)-alkyl, -O-C(O)-alkyl, and -C(O)-alkyl.

For certain embodiments, R_1 and R' join together to form a ring system. The size and components of the ring system are not limiting as long as they do not destroy the immunomodulator activity of the compound (i.e., they are non-interfering). Typically, this means that the ring system is a monocyclic ring system containing 5 to 8 atoms in the ring or a bicyclic ring system containing 9 to 11 atoms in the rings. For certain embodiments, the ring system contains one or two saturated or unsaturated rings. For certain embodiments, the ring system contains one or two heteratoms (e.g., O, S, N).

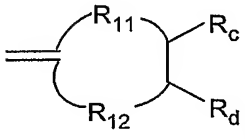
The ring system is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, alkylene-aryl, and -C(O)-alkyl. Also, one of skill in the art would understand that the ring system would not include an aromatic ring attached to the N=C moiety.

For certain embodiments, R_1 and R' join to form a ring system selected from the group consisting of cyclopentyl, cyclohexyl, cycloheptyl, piperidinyl, and indanyl.

For certain embodiments, R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and

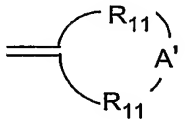


wherein the total number of atoms in the ring is 4 to 9.

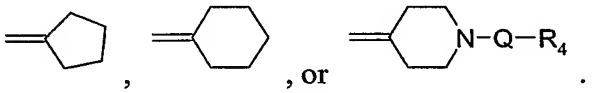
For certain embodiments, at least one of R' or R_1 is hydrogen. For certain embodiments, at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted. For certain embodiments, at least one of R' or R_1 is aryl or substituted

aryl and at least one of R' or R_1 is hydrogen. For certain embodiments, at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

For certain embodiments, R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl. For such embodiments, preferably, the ring system is



For certain embodiments, R_1 and R' are each methyl.

For certain embodiments, R" is hydrogen or a non-interfering substituent. For certain embodiments, R" is selected from the group consisting of: -R_4, -X'-R_4, -X'-Y-R_4, and -X'-R_5. For certain embodiments, R" is hydrogen, alkoxyalkylenyl, -R_4, -X'-R_4, or -X'-Y-R_4. For certain of these embodiments, preferably, X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-; and R_4 is alkyl.

For certain embodiments, R" is selected from the group consisting of: hydrogen, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, alkylene-Y"-alkyl, alkylene-Y"- alkenyl, alkylene-Y"-aryl, and alkyl or alkenyl substituted by one or more substituents selected from the group consisting of: hydroxyl, halogen, -N(R_{8a})$_2$, -C(O)-C_{1-10} alkyl, -C(O)-O-C_{1-10} alkyl, -N_3, aryl, heteroaryl, heterocyclyl, -C(O)-aryl, and -C(O)-heteroaryl. For these embodiments, Y" is –O– or –$S(O)_{0-2}$-.

For certain embodiments, R" is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl (i.e., alkylene-O-alkyl). For certain embodiments, R" is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

For certain embodiments, R_2 is selected from the group consisting of: -R_4,

-X'-R_4, -X'-Y-R_4, and -X'-R_5. For certain embodiments, R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X'-R_4, or -X'-Y-R_4. For certain of these embodiments, preferably, X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, or -$C(R_6)$-$N(OR_9)$-; and R_4 is alkyl.

For certain embodiments, R_2 is selected from the group consisting of: hydrogen, alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, alkylene-Y"-alkyl, alkylene-Y"- alkenyl, alkylene-Y"-aryl, and alkyl or alkenyl substituted by one or more substituents selected from the group consisting of: hydroxyl, halogen, -$N(R_{8a})_2$, -C(O)-C_{1-10} alkyl, -C(O)-O-C_{1-10} alkyl, -N_3, aryl, heteroaryl, heterocyclyl, -C(O)-aryl, and -C(O)-heteroaryl. For these embodiments, Y" is –O– or –$S(O)_{0-2}$-.

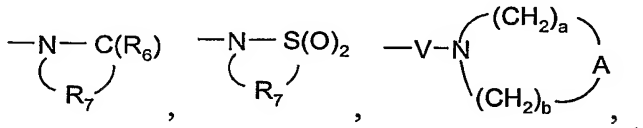
For certain embodiments, R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl (i.e., alkylene-O-alkyl). For certain embodiments, R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

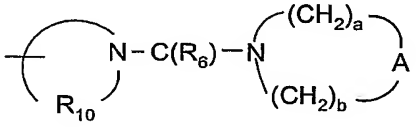
For certain embodiments, R_3 is selected from the group consisting of: -Z-R_4, -Z-X'-R_4, -Z-X'-Y-R_4, and -Z-X'-R_5. For certain embodiments, R_3 is phenyl, pyridin-3-yl, pyridin-4-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, 3-(morpholine-4-carbonyl)phenyl, or 3-(*N,N*-dimethylaminocarbonyl)phenyl. For certain of these embodiments, m is 1.

For certain embodiments, each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl,

amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo. For certain embodiments, R_4 is alkyl.

For certain embodiments, each R_5 is independently selected from the group consisting of:



and  .

For certain embodiments, each R_6 is independently selected from the group consisting of =O and =S.

For certain embodiments, each R_7 is independently C_{2-7} alkylene.

For certain embodiments, each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl.

For certain embodiments, each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

For certain embodiments, each R_9 is independently selected from the group consisting of hydrogen and alkyl.

For certain embodiments, R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups.

For certain embodiments, each R_{10} is independently C_{3-8} alkylene.

For certain embodiments, each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom.

For certain embodiments, R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom.

For certain embodiments, R_A and R_B are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

For certain embodiments, R_A and R_B are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$; or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group; or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups. In certain of these embodiments the fused aryl ring is a benzene ring. In certain of these embodiments the heteroaryl ring is a pyridine ring. In certain of these embodiments the saturated ring is a cyclohexane ring. In certain of these embodiments the saturated ring is a piperidine ring.

For certain embodiments, R_A and R_B form a fused aryl ring or heteroaryl ring containing one N, wherein the aryl ring or heteroaryl ring is unsubstituted. In certain of these embodiments the fused aryl ring is a benzene ring. In certain of these embodiments the heteroaryl ring is a pyridine ring. For certain embodiments, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one N, wherein the saturated ring is unsubstituted. In certain of these embodiments the saturated ring is a cyclohexane ring. In certain of these embodiments the saturated ring is a piperidine ring.

For certain embodiments, R_{A1} and R_{B1} are each independently selected from the group consisting of: hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. For certain embodiments, R_{A1} and R_{B1} are each methyl.

For certain embodiments, R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

For certain embodiments, each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$.

For certain embodiments, A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$. For certain embodiments A' is $-N(-Q-R_4)-$ or $-CH_2-$.

For certain embodiments, E is selected from the group consisting of CH, CR, CR_3, and N. In certain embodiments, when E is CR_3, then m is 0 and n is 0 or 1. In certain embodiments, when E is CR and m is 1, n is 0. Preferably, E is CH or N.

For certain embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$. For certain embodiments, Q is a bond or -C(O)-.

For certain embodiments, each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$.

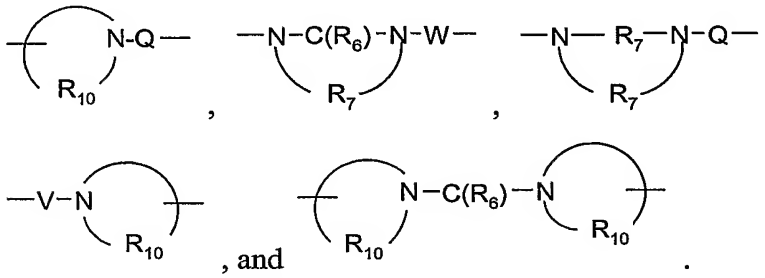
For certain embodiments, W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$.

For certain embodiments, X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups. For certain embodiments, X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-. For certain embodiments, X is $-CH(R_{9a})$-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups. For certain embodiments, X is $-C_{3-5}$ alkylene- or $-CH_2CH_2OCH_2CH_2-$. For certain

embodiments, X is -CH(R_{9a})-C_{1-5} alkylene- and for other embodiments X is propylene or butylene.

For certain embodiments, each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups. For certain embodiments, each X' is independently C_{1-2} alkylene.

For certain embodiments, each Y is independently selected from the group consisting of: -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, -C(R_6)-N(OR_9)-,



For certain embodiments, each Y is independently -S(O)$_{0-2}$-, -S(O)$_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-.

For certain embodiments, Y" is –O– or –S(O)$_{0-2}$-.

For certain embodiments, Z is a bond or -O-. Preferably, Z is a bond.

For certain embodiments, n is an integer from 0 to 4. For certain embodiments, n is an integer from 0 to 3. For certain embodiments, n is 0 or 1. For certain embodiments, n is 0.

For certain embodiments, m is 0 or 1. For certain embodiments, m is 1.

For certain embodiments, when m is 1, n is 0 or 1.

For certain embodiments, when m is 0, n is 0 or 1.

For certain embodiments, m and n are each 0.

For certain embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

As used herein, the terms "alkyl," "alkenyl," "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene," "-alkylene-", "alkenylene", "-alkenylene-", "alkynylene", and "-alkynylene-" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms "alkylenyl", "alkenylenyl", and "alkynylenyl" are used when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an "alkylene" moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of alkyl groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

The term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl,

tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl, homopiperazinyl, and the like.

The terms "arylene", "heteroarylene", and "heterocyclylene" are the divalent forms of the "aryl", "heteroaryl", and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene", "heteroarylene", and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-N(R_9)_2$ each R_9 group is independently selected. In another example, when an R_2 and an R_3 group both contain an R_4 group, each R_4 group is independently selected. In a further example, when more than one Y group is present (i.e., R_2 and R_3 both contain a Y group) and each Y group contains one or more R_8 groups, then each Y group is independently selected, and each R_8 group is independently selected.

The invention is inclusive of the compounds described herein and salts thereof in any of their pharmaceutically acceptable forms, including isomers such as diastereomers and enantiomers, solvates, polymorphs, and the like. In particular, if

a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I where R, R', R_1, R_2, m, and X are as defined above; E' is carbon (imidazoquinoline ring) or nitrogen (imidazonaphthyridine ring); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring) with the proviso that when m is 1, n is 0 or 1; and D is –Br, –I, or $–OCH_2Ph$, wherein Ph is phenyl. In step (1) of Reaction Scheme I, an aniline or aminopyridine of Formula XX is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XXI. The reaction is conveniently carried out by adding a solution of an aniline or aminopyridine of Formula XX to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature. The product can be isolated using conventional methods. Many anilines and aminopyridines of Formula XX are commercially available; others can be prepared by known synthetic methods. For example, benzyloxypyridines of Formula XX can be prepared using the method of Holladay et al., *Biorg. Med. Chem. Lett.*, *8*, pp. 2797-2802, (1998).

In step (2) of Reaction Scheme I, an imine of Formula XXI undergoes thermolysis and cyclization to provide a compound of Formula XXII. The reaction is conveniently carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature between 200 and 250 °C. The product can be isolated using conventional methods.

In step (3) of Reaction Scheme I, a compound of Formula XXII is nitrated under conventional nitration conditions to provide a compound of Formula XXIII. The reaction is conveniently carried out by adding nitric acid to the compound of Formula XXII in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature. The product can be isolated using conventional methods.

In step (4) of Reaction Scheme I, a 3-nitro[1,5]naphthyridin-4-ol or 3-nitroquinolin-4-ol of Formula XXIII is chlorinated using conventional chlorination chemistry to provide a 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XXIV. The reaction is conveniently carried out by treating the compound of Formula XXIII with phosphorous oxychloride in a suitable solvent such as *N*,*N*-dimethylformamide (DMF). The reaction can be carried out at ambient temperature or at an elevated temperature such as 100 °C, and the product can be isolated using conventional methods.

In step (5) of Reaction Scheme I, a 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XXIV is treated with an amine of Formula HO-X-NH_2 to provide a compound of Formula XXV. Several amines of Formula HO-X-NH_2 are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding the amine of Formula HO-X-NH_2 to a solution of the 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XXIV in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as, for example, 0 °C. The reaction product can be isolated using conventional methods.

In step (6) of Reaction Scheme I, a compound of Formula XXV is reduced to provide a diamine of Formula XXVI. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as palladium on carbon or platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, acetonitrile, or ethyl acetate. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

Alternatively, the reduction in step (6) can be carried out using a one- or two-phase sodium dithionite reduction. The reaction is conveniently carried out using the conditions described by Park, K. K.; Oh, C. H.; and Joung, W. K.; *Tetrahedron Lett.*, *34*, pp. 7445-7446 (1993) by adding sodium dithionite to a compound of Formula XXV in a mixture of dichloromethane and water at ambient

temperature in the presence of potassium carbonate and ethyl viologen dibromide, ethyl viologen diiodide, or 1,1'-di-*n*-octyl-4,4'-bipyridinium dibromide. The product can be isolated using conventional methods.

In step (7) of Reaction Scheme I, a diamine of Formula XXVI, is reacted with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVII. Suitable carboxylic acid equivalents include orthoesters of Formula $R_2C(O\text{-alkyl})_3$, 1,1-dialkoxyalkyl alkanoates of Formula $R_2C(O\text{-alkyl})_2(O\text{-}C(O)\text{-alkyl})$, and acid chlorides of Formula $R_2C(O)Cl$. The selection of the carboxylic acid equivalent is determined by the desired substituent at R_2. For example, triethyl orthoformate will provide a compound where R_2 is hydrogen, and trimethyl orthobutyrate will provide a compound where R_2 is a propyl group. Step (7) is conveniently carried out by adding the carboxylic acid equivalent to a diamine of Formula XXVI in a suitable solvent such as toluene or xylenes. Optionally, catalytic pyridine hydrochloride can be added. The reaction is carried out at a temperature high enough to drive off alcohol or water formed during the reaction. Conveniently, a Dean-Stark trap can be used to collect the volatiles. The 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline product of Formula XXVII can be isolated and optionally purified using conventional techniques.

Alternatively, step (7) of Reaction Scheme I can be carried out in two steps when an acid chloride of Formula $R_2C(O)Cl$ is used as the carboxylic acid equivalent. Part (i) of step (7) is conveniently carried out by adding the acid chloride to a solution of a diamine of Formula XXVI in a suitable solvent such as dichloromethane or acetonitrile. Optionally, a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine can be added. The reaction can be carried out at ambient temperature. The amide product can be isolated and optionally purified using conventional techniques. Part (ii) of step (7) involves heating the amide prepared in part (i) in the presence of base to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVII. The reaction is conveniently carried out in a suitable solvent such as ethanol in the

presence of a base such aqueous sodium hydroxide or aqueous potassium carbonate at elevated temperature. The product of Formula XXVII can be isolated using conventional methods.

In an alternative route to a compound of Formula XXVII, the alcohol group in a compound of Formula XXV is first protected with an appropriate protecting group such as an acetyl group. The protection reaction is conveniently carried out by adding acetic anhydride to a solution of a compound of Formula XXV in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine optionally with 4-dimethylaminopyridine as a catalyst. The reaction is carried out at a sub-ambient temperature such as, for example, 0 °C. The reaction product can be isolated using conventional methods and is then subjected to the conditions described in steps (6) and (7) of Reaction Scheme I. If the two-step procedure employing an acid chloride as the carboxylic acid equivalent is used in step (7), the acetyl protecting group is cleaved under the conditions described in part (ii) of step (7) to afford a compound of the Formula XXVII. If the carboxylic acid equivalent is introduced using the one-step procedure described in step (7), the acetyl protecting group can be cleaved in a subsequent reaction to afford a compound of the Formula XXVII. Cleavage of the acetyl group is conveniently carried out using a base such as potassium carbonate in a suitable solvent such as methanol. The reaction is carried out at ambient temperature and the product of Formula XXVII can be isolated using conventional methods.

Several compounds of Formula XXVII, wherein m and n are both 0, are known and have been prepared by other related routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 6,194,425 (Gerster et al.), 5,605,899 (Gerster et al.), and 5,175,296 (Gerster).

In step (8) of Reaction Scheme I, a hydroxy-substituted compound of Formula XXVII is treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected hydroxylamine of Formula XXVIII. The reaction is conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of the alcohol of Formula XXVII in a suitable

solvent such as tetrahydrofuran or DMF and then slowly adding diisopropyl azodicarboxylate. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 60 °C. The product can be isolated using conventional methods.

In step (9) of Reaction Scheme I, an *N*-phthalimide-protected hydroxylamine of Formula XXVIII is oxidized to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide or 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXIX using a conventional oxidizing agent capable of forming *N*-oxides. The reaction is conveniently carried out by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXVIII in a solvent such as chloroform or dichloromethane. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

In step (10) of Reaction Scheme I, a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-5*N*-oxide or 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXIX is aminated to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXX. Step (10) involves the activation of an *N*-oxide of Formula XXIX by conversion to an ester and then reacting the ester with an aminating agent. Suitable activating agents include alkyl- or arylsulfonyl chlorides such as benzenesulfonyl chloride, methanesulfonyl chloride, or *p*-toluenesulfonyl chloride. Suitable aminating agents include ammonia, in the form of ammonium hydroxide, for example, and ammonium salts such as ammonium carbonate, ammonium bicarbonate, and ammonium phosphate. The reaction is conveniently carried out by adding ammonium hydroxide to a solution of the *N*-oxide of Formula XXIX in a suitable solvent such as dichloromethane or chloroform and then adding *p*-toluenesulfonyl chloride. The reaction can be carried out at ambient temperature. Under these reaction conditions, the *N*-phthalimide protecting group is removed to provide the 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXX or a pharmaceutically acceptable salt thereof, which can be isolated from the reaction mixture using conventional methods.

Steps (9) and (10) can alternatively be combined and carried out as a one-pot procedure by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula XXVIII in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride without isolating the *N*-oxide of Formula XXIX. The product of Formula XXX or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (11) of Reaction Scheme I, the hydroxylamine group in a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXX reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide an oxime of Formula XXXI, which is a subgenus of Formulas I and II. Numerous aldehydes and ketones of Formula $R_1C(O)R'$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of Formula $R_1C(O)R'$ to a solution of the hydroxylamine of Formula XXX in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature, or at elevated temperature. Optionally, an acid such as pyridine hydrochloride can be added. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of the invention can also be prepared from the compound of Formula XXVII by an alternative route shown as Route 2 in Reaction Scheme I. In step (8a) of Reaction Scheme I an alcohol of Formula XXVII is converted to a hydroxylamine of Formula XXXII, which is a subgenus of Formula X. The reaction is carried out under Mitsunobu reaction conditions as described for step (8) of Route 1, and during the isolation of the reaction product, the *N*-phthalimide protecting group is removed by treatment with a strong base. Conveniently, an acidic aqueous solution of a *N*-phthalimide-protected hydroxylamine prepared from a compound of Formula XXVII is treated with sodium hydroxide until the pH of the solution is basic. The hydroxylamine of Formula XXXII can then be isolated using conventional methods.

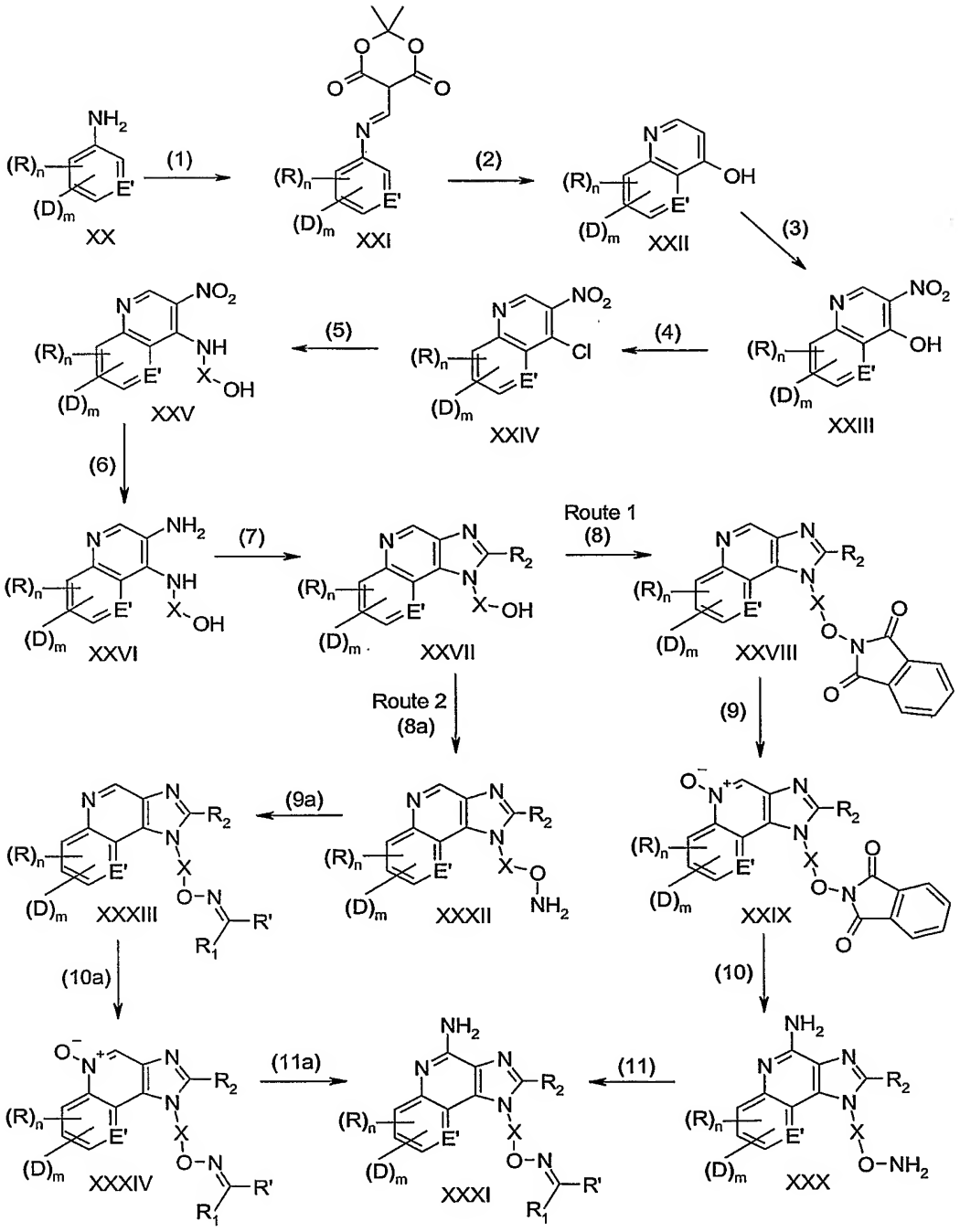
In step (9a) of Reaction Scheme I, a hydroxylamine of Formula XXXII reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide an oxime of Formula XXXIII, a subgenus of Formula XII. Numerous aldehydes and ketones of Formula $R_1C(O)R'$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be carried out as described above in step (11) of Route 1.

In step (10a) of Reaction Scheme I, a compound of Formula XXXIII is oxidized to provide an *N*-oxide of Formula XXXIV, a subgenus of Formula XIV, using a conventional oxidizing agent capable of forming *N*-oxides. The reaction can be carried out as described above in step (9) of Route 1.

In step (11a) of Reaction Scheme I, a *N*-oxide of Formula XXXIV is aminated to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXI. The reaction can be carried out as described above in step (10) of Route 1. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

For some embodiments, compounds in Reaction Scheme I can be further elaborated using known synthetic methods. For example, the acid chloride used in step (7) of Reaction Scheme I may contain a protected hydroxy or amino group. Some acid chlorides of this type, for example acetoxyacetyl chloride, are commercially available. Others can be prepared by known synthetic methods. The protected hydroxy or amino group may be deprotected and further functionalized before step (9) of Route 1 of Reaction Scheme I. For examples of this type of functionalization of an R_2 group, see U.S. Patent No. 5,389,640 (Gerster et al.).

Reaction Scheme I



Compounds of the invention can also be prepared according to Reaction Scheme II, wherein R, R', R_1, R_2, E', and X are as defined above; n is 0 or 1; R_{3a} is -O-R_{4a}, -O-X'-R_4, -O-X'-Y-R_4, or -O-X'-R_5; wherein R_4, R_5, X' and Y are as defined above, and R_{4a} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R_4 above. Compounds of Formula XXXa are a subset of compounds of Formula XXX, defined in Reaction Scheme I, wherein D is $-OCH_2Ph$. In step (1) of Reaction Scheme II, the benzyl group in a benzyloxy-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXa is cleaved to provide a compound of Formula XXXb. The cleavage is conveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium or platinum on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation is conveniently carried out by adding ammonium formate to a solution of a compound of Formula XXXa in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the refluxing temperature of the solvent. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2) of Reaction Scheme II, the hydroxylamine group in a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXb reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide an oxime of Formula XXXIa, a subgenus of Formulas I and II. The reaction can be carried out as described above in step (11) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

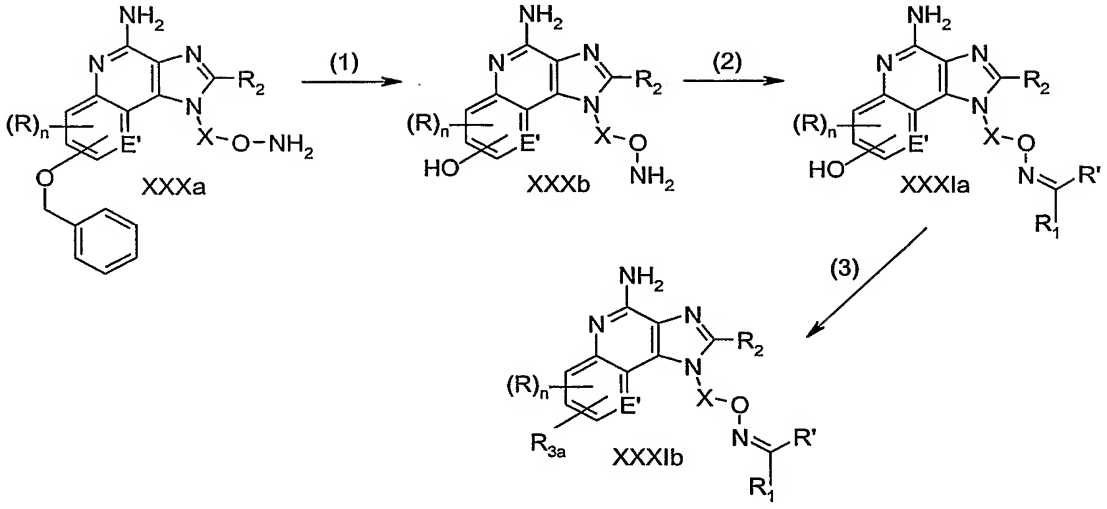
In step (3) of Reaction Scheme II, a hydroxy-substituted compound of Formula XXXIa is converted to an ether-substituted compound of Formula XXXIb using a Williamson-type ether synthesis. The reaction is effected by treating a compound of Formula XXXIa with an aryl or alkyl halide of Formula Halide-R_{4a},

Halide-alkylene-R_4, Halide-alkylene-Y-R_4 or Halide-alkylene-R_5 in the presence of a base. Numerous alkyl or aryl halides of these formulas are commercially available, including substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, and substituted fluorobenzenes. Other alkyl or aryl halides of these Formulas can be prepared using conventional synthetic methods. The reaction is conveniently carried out by combining a reagent of Formula Halide-R_{4a}, Halide-alkylene-R_4, Halide-alkylene-Y-R_4 or Halide-alkylene-R_5 with a hydroxy-substituted compound of Formula XXXIa in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. Optionally, catalytic tetrabutylammonium bromide can be added. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C, depending on the reactivity of the aryl or alkyl halide. The product of Formula XXXIb, which is a subgenus of Formulas I and II, or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, step (3) may be carried out using the Ullmann ether synthesis, in which an alkali metal aryloxide of a compound of Formula XXXIa reacts with an aryl halide in the presence of copper salts, to provide a compound of Formula XXXIb, where R_{3a} is –O–R_{4a},–O–X'–R_4, or –O–X'–Y-R_4, wherein X' is an arylene or heteroarylene. Numerous substituted and unsubstituted aryl halides are commercially available; others can be prepared using conventional methods.

Compounds of the Formula XXXIb may also be obtained using an alternative five step procedure starting from a compound of Formula XXXII, shown in Reaction Scheme I. The methods described in steps (1), (2), and (3) of Reaction Scheme II can be sequentially carried out on a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXII, wherein D is a benzyloxy group. The product can then be converted into a compound of Formula XXXIb according to the reaction conditions described in steps (9) and (10) of Reaction Scheme I.

Reaction Scheme II



Compounds of the invention can also be prepared according to Reaction Scheme III, wherein R, R', R_1, R_2, E', and X are as defined above; Hal is –Br or –I; n is 0 or 1; and R_{3b} and R_{3c} are as defined below. Formula XXXc is a subset of Formula XXX, defined in Reaction Scheme I, wherein D is –Br or –I. Step (1) of Reaction Scheme III can be carried out using known palladium-catalyzed coupling reactions such as the Suzuki coupling and the Heck reaction. For example, a halogen substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXc undergoes Suzuki coupling with a boronic acid of Formula R_{3b}-$B(OH)_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3b}-$B(O\text{-alkyl})_2$ to provide a compound of Formula XXXd; wherein R_{3b} is -R_{4a}, -X'_a-R_4, -X'_b-Y-R_4, or -X'_b-R_5; where X'_a is alkenylene; X'_b is arylene, heteroarylene, or alkenylene interrupted or terminated by arylene or heteroarylene; and R_4, R_{4a}, R_5, and Y are as defined above. The coupling is carried out by combining a compound of Formula XXXc with a boronic acid or an ester or anhydride thereof in the presence of palladium (II) acetate, triphenylphosphine, and a base such as sodium carbonate in a suitable solvent such as *n*-propanol. The reaction can be carried out at an elevated temperature, for example, at the reflux

temperature. Numerous boronic acids of Formula R_{3b}-$B(OH)_2$, anhydrides thereof, and boronic acid esters of Formula R_{3b}-B(O-alkyl)$_2$ are commercially available; others can be readily prepared using known synthetic methods. See, for example, Li, W. et al, *J. Org. Chem.*, *67*, pp. 5394-5397 (2002). The product of Formula XXXd or a pharmaceutically acceptable salt thereof can be isolated by conventional methods.

The Heck reaction can also be used in step (1) of Reaction Scheme III to provide compounds of Formula XXXd, wherein R_{3b} is -X'_a-R_{4a} and -X'_a-Y-R_4. The Heck reaction is carried out by coupling a compound of Formula XXXc with a compound of the Formula H_2C=C(H)-R_{4a} or H_2C=C(H)-Y-R_4. Several of these vinyl-substituted compounds are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the compound of Formula XXXc and the vinyl-substituted compound in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine in a suitable solvent such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature such as 100-120 °C under an inert atmosphere. The product of Formula XXXd or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula XXXd, wherein R_{3b} is -X'_c-R_4, X'_c is alkynylene, and R_4 is as defined above, can also be prepared by palladium catalyzed coupling reactions such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a compound of Formula XXXc with a compound of the Formula (alkyl)$_3$Sn-C≡C-R_4, (alkyl)$_3$Si-C≡C-R_4, or H-C≡C-R_4.

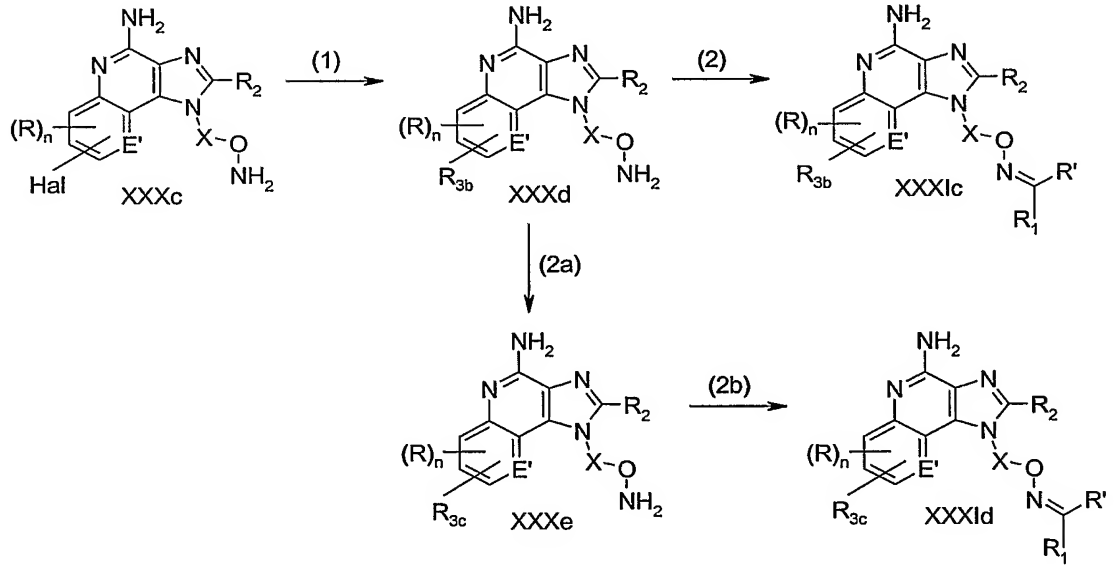
In step (2) of Reaction Scheme III, the hydroxylamine group in a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXd reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide an oxime of Formula XXXIc, a subgenus of Formulas I and II. The reaction can be carried out as described above in step (11) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of the invention, wherein R_{3c} is $-X'_d-R_4$, $-X'_d-Y-R_4$, $-X'_e-Y-R_4$, or $-X'_e-R_5$, where X'_d is alkylene; X'_e is alkylene interrupted or terminated by arylene or heteroarylene; and R_4, R_5, and Y are as defined above, can be prepared as shown in steps (2a) and (2b) of Reaction Scheme III. In step (2a) of Reaction Scheme III, a compound of Formula XXXd, wherein R_{3b} is $-X'_a-R_4$, $-X'_a-Y-R_4$, $-X'_b-Y-R_4$, $-X'_b-R_5$, or $-X'_c-R_4$, where X'_b is alkenylene interrupted or terminated by arylene or heteroarylene, and X'_a, X'_c, Y, R_4, and R_5 are as defined above, is reduced to provide a compound of Formula XXXe. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods. Step (2b) of Reaction Scheme III can be carried out as described above in step (11) of Reaction Scheme I to provide a compound of the Formula XXXId, a subgenus of Formulas I and II.

Compounds of the Formula XXXIc and XXXId can be obtained using other routes. For example, the methods described in step (1) of Scheme III can be carried out on a *N-tert*-butoxycarbonyl-protected hydroxylamine derivative of Formula XXXc, which can be synthesized from a compound of Formula XXXc using conventional chemistry. The reaction product can undergo deprotection of the *tert*-butoxycarbonyl group using a conventional method and the chemistry described in step (2) or steps (2a) and (2b) can be applied to afford a compound of Formula XXXIc or XXXId, respectively. In addition, several of the compounds shown in Reaction Scheme I such as compounds of the Formula XXVII, XXVIII, XXXI, XXXII, and XXXIII, or appropriately protected derivatives thereof, wherein D is –Br or –I, could be used as substrates for the metal-mediated coupling chemistry described above in step (1) of Reaction Scheme III. The synthesis of compounds of Formula XXXIc or XXXId can be completed using the appropriate steps in Reaction Schemes I and III, with the addition of a deprotection step if necessary. For example, a compound of Formula XXXII wherein D is –Br or –I can be treated

with di-*tert*-butyl dicarbonate to afford an *N*-*tert*-butoxycarbonyl-protected hydroxylamine compound of Formula XXXII that can undergo the metal-mediated coupling chemistry described in step (1) of Reaction Scheme III. The removal of the *tert*-butyloxycarbonyl group using conventional methods can be followed by the methods described in steps (9a), (10a), and (11a) of Reaction Scheme I to provide a compound of Formula XXXIc. Conveniently, a compound of Formula XXXI, wherein D is -Br or -I, can be subjected to the cross-coupling reaction conditions described in step (1) of Reaction Scheme III to provide a compound of Formula XXXIc, which may be reduced, when appropriate, according to the conditions described in step (2a) of Reaction Scheme III to provide a compound of Formula XXXId.

Reaction Scheme III



Tetrahydroquinolines and tetrahydronaphthyridines of the invention can be prepared according to Reaction Scheme IV, wherein E', X, R', and R_1 are as defined above; n is an integer from 0 to 4 (imidazoquinoline ring system) or 0 to 3

(imidazonaphthyridine ring system); R_a is alkyl, alkoxy, or $-N(R_9)_2$; and R_{2a} is a subset of R_2 as defined above that does not include those substituents that one skilled in the art would recognize as being susceptible to reduction under the acidic hydrogenation conditions of step (2). These susceptible groups include, for example, alkenyl, alkynyl, and aryl groups and groups bearing nitro substituents.

In step (1) of Reaction Scheme IV, a hydroxy-substituted compound of Formula XXVIIa is oxidized and aminated to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXXV. Compounds of Formula XXVIIa can be prepared as shown in Reaction Scheme I. The oxidation and amination can be carried out as described in steps (9) and (10) of Reaction Scheme I.

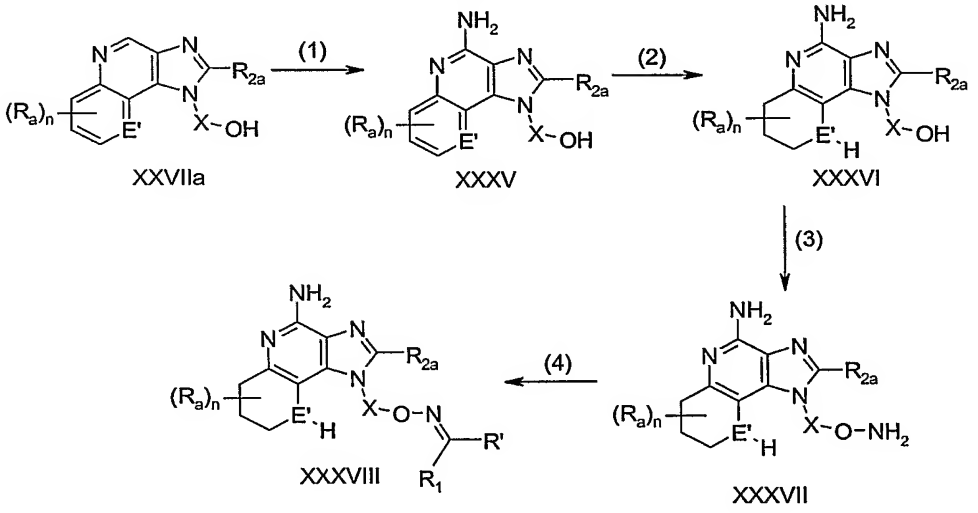
In step (2) of Reaction Scheme IV, a compound of Formula XXXV is reduced to a 6,7,8,9-tetrahydro compound of Formula XXXVI. The reaction is conveniently carried out under hetereogeneous hydrogenation conditions by adding platinum (IV) oxide to a solution of the compound of Formula XXXV in trifluoroacetic acid and placing the reaction under hydrogen pressure. The reaction can be carried out on a Parr apparatus at ambient temperature. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (3) of Reaction Scheme V, a hydroxy-substituted compound of Formula XXXVI is converted to a hydroxylamine of Formula XXXVII. The reaction is carried out under the Mitsunobu reaction conditions as described for step (8) of Reaction Scheme I, and during the isolation of the reaction product, the *N*-phthalimide protecting group is removed by treatment with a strong base. Conveniently, an acidic aqueous solution of a *N*-phthalimide-protected hydroxylamine prepared from a compound of Formula XXXVI is treated with sodium hydroxide until the pH of the solution is basic. The hydroxylamine of Formula XXXVII can then be isolated using conventional methods. Alternatively, the Mitsunobu reaction can be carried out as described in step (8) of Reaction Scheme I to provide a *N*-phthalimide-protected hydroxylamine, which can be treated with hydrazine in a suitable solvent such as ethanol at ambient temperature

to provide a hydroxylamine of Formula XXXVII. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (4) Reaction Scheme IV, the hydroxylamine group in a compound of Formula XXXVII reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide an oxime of Formula XXXVIII, a subgenus of Formulas I and II. The reaction can be carried out as described above in step (11) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

Reaction Scheme IV



For some embodiments, compounds of the invention are prepared according to Reaction Scheme V, where Ph, R', R_1, R_2, R_{A1}, R_{B1}, and X are as defined above. In step (1) of Reaction Scheme V, a 2,4-dichloro-3-nitropyridine of Formula XXXIX is reacted with an amino alcohol of the Formula H_2N-X-OH to form a 2-chloro-3-nitropyridine of Formula XL. The reaction is conveniently carried out by combining an amino alcohol of Formula H_2N-X-OH and a 2,4-dichloro-3-nitropyridine of Formula XXXIX in the presence of a base such as triethylamine in an inert solvent such as DMF. The reaction can be carried out at ambient

temperature, and the product can be isolated from the reaction mixture using conventional methods. Several amines of Formula HO-X-NH_2 are commercially available; others can be prepared by known synthetic methods. Many 2,4-dichloro-3-nitropyridines of the Formula XXXIX are known and can be readily prepared using known synthetic methods. (See, for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein.)

In step (2) of Reaction Scheme V, a 2-chloro-3-nitropyridine of Formula XL is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XLI. The reaction can be carried out by combining the compound of Formula XL with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium(III) chloride, preferably cerium(III) chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction can be carried out by combining the compound of Formula XL with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50-60 °C, optionally in the presence of ammonium chloride. The product can be isolated from the reaction mixture using conventional methods.

In step (3) of Reaction Scheme V, an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula XLI is reduced to provide a compound of Formula XLII. The reduction can be carried out as described in step (6) of Reaction Scheme I.

In step (4) of Reaction Scheme V, a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula XLII is reacted with a carboxylic acid equivalent to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XLIII. The reaction can be carried out as described in step (7) of Reaction Scheme I.

A compound of Formula XLIII can also be prepared from a compound of Formula XLI, wherein the alcohol group in a compound of Formula XLI is first protected with an appropriate protecting group such as an acetyl group. The incorporation of the acetyl group, subsequent reduction and cyclization, and removal of the acetyl group is described in Reaction Scheme I.

In step (5) of Reaction Scheme V, a hydroxy-substituted compound of Formula XLIII is treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected hydroxylamine of Formula XVI. The reaction is carried out as described for step (8) of Route 1 of Reaction Scheme I.

In step (6) of Reaction Scheme V, the *N*-phthalimide-protected hydroxylamine of Formula XVI is treated with hydrazine in a suitable solvent such as ethanol to provide a hydroxylamine of Formula XVII. The reaction can be carried out at ambient temperature and the product can be isolated from the reaction mixture using conventional methods.

In step (7) Reaction Scheme V, the hydroxylamine group in a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVII reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide an oxime of Formula XVIII. The reaction can be carried out as described above in step (11) of Reaction Scheme I.

In step (8) of Reaction Scheme V, the tetrazolo ring can be removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula XVIII by reaction with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula XLIV. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature.

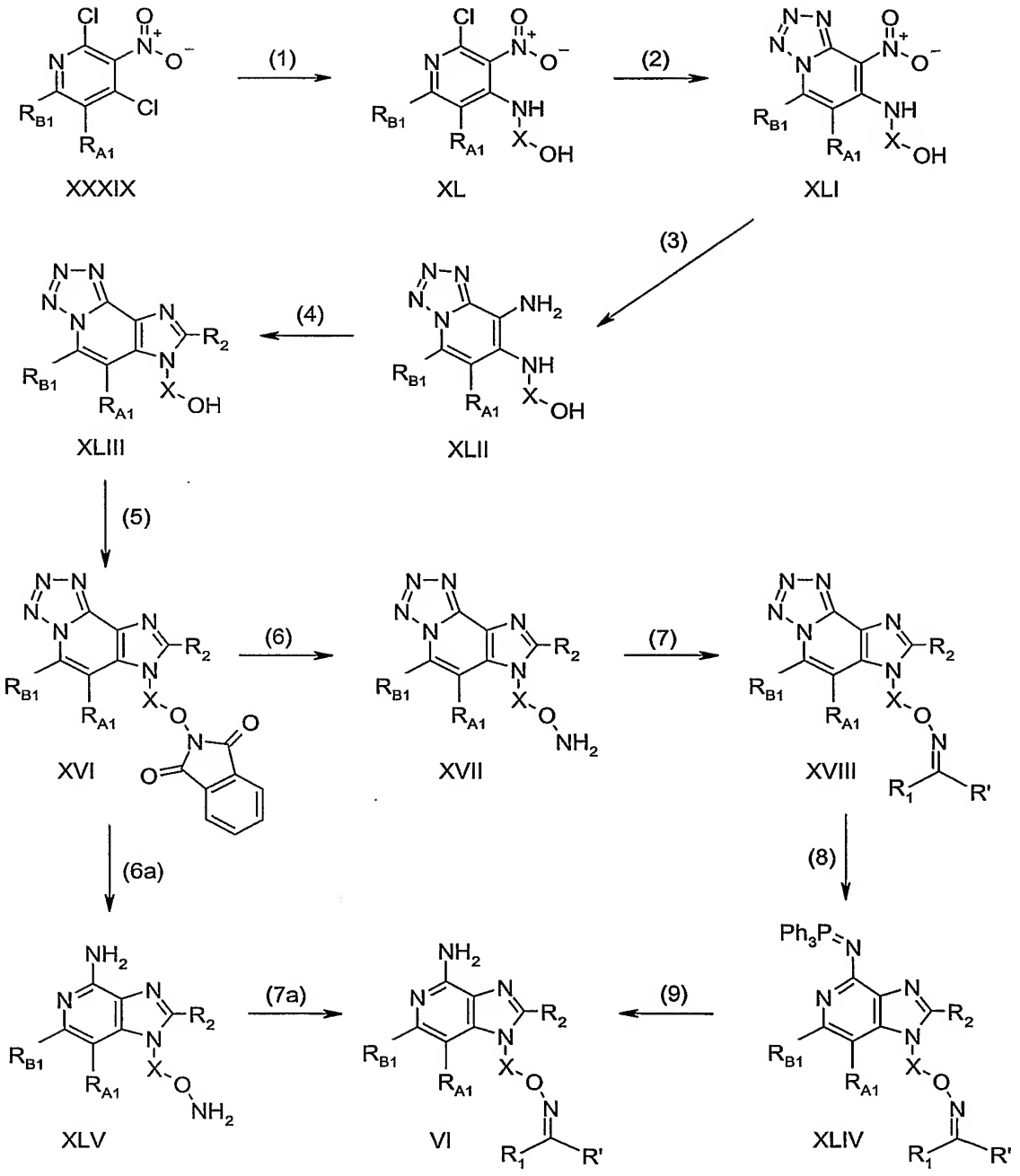
In step (9) of Reaction Scheme V, an *N*-triphenylphosphinyl intermediate of Formula XLIV is hydrolyzed to provide an oxime-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula VI. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol in the presence of an acid such as trifluoroacetic acid or hydrochloric acid. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula VI or as a pharmaceutically acceptable salt thereof.

A compound of the Formula VI or a pharmaceutically acceptable salt thereof may also be obtained through an alternative route from a compound of Formula XVI. In step (6a) of Reaction Scheme V, a compound of Formula XVI is treated

according to the reaction conditions described in steps (8) and (9) of Reaction Scheme V using hydrochloric acid as the acid in step (9). Under these reaction conditions, the *N*-phthalimide is removed to provide the hydroxylamine-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula XLV. The product can be isolated and purified using conventional methods.

In step (7a) of Reaction Scheme V, a hydroxylamine-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula XLV reacts with an aldehyde or ketone of Formula $R_1C(O)R'$ to provide an oxime of Formula VI. The reaction can be carried out as described above in step (11) of Reaction Scheme I. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula VI or as a pharmaceutically acceptable salt thereof.

Reaction Scheme V



Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound sufficient to induce a therapeutic or prophylactic effect, such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon-α (IFN-α) and/or

tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. The animal to which the compound or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound may provide therapeutic treatment. Alternatively, the compound may be administered to the animal prior to the animal acquiring the disease so that administration of the compound may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ can be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 can be inhibited upon administration of the compounds.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or composition may be administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound and other component or components may be administered separately;

together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, renal cell carcinoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple

myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers; and

(e) T_H2-mediated, atopic, and autoimmune diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, Ommen's syndrome, discoid lupus, alopecia areata, inhibition of keloid formation and other types of scarring, and enhancing would healing, including chronic wounds.

IRMs identified herein also may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; recombinant proteins; glycoproteins; peptides; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

IRMs may also be particularly helpful in individuals having compromised immune function. For example, IRM compounds may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages,

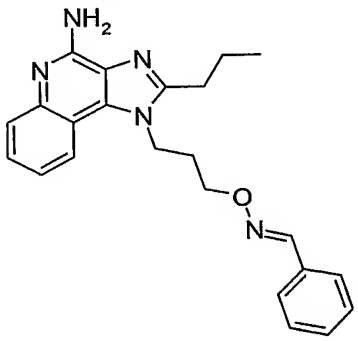
dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

Example 1

(1*E*)-Benzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



Part A

A solution of 3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propan-1-ol (20.0 grams (g), 74.3 millimoles (mmol)) in tetrahydrofuran (300 milliliters (mL)) was cooled to approximately 0 °C; triphenylphosphine (23.4 g, 89.1 mmol) and *N*-hydroxyphthalimide (14.5 g, 89.1 mmol) were then added. After five minutes of stirring, diisopropyl azodicarboxylate (17.5 mL, 89.1 mmol) was added dropwise over a period of 15 minutes (min). The reaction was allowed to warm to room temperature and stirred overnight. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (300 mL). A solution of hydrochloric acid (150 mL of 6 molar (M)) was then added, and approximately 50 mL of the solvent was removed under reduced pressure to provide a white precipitate, which was stirred for ten minutes and isolated by filtration. Additional salt eventually precipitated from the filtrate and was isolated by filtration. Chloroform (300 mL) and water (300 mL) were added to the salt, and solid sodium bicarbonate was added to the mixture to adjust to pH 8. The organic solution was then dried over magnesium sulfate, filtered, and concentrated under reduced

pressure to provide 28.4 g of 2-[3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.3 (s, 1H), 8.3 (m, 2H), 7.9 (m, 2H), 7.8 (m, 2H), 7.6 (m, 2H), 5.0 (t, J = 7.3 Hz, 2H), 4.4 (t, J = 5.3 Hz, 2H), 3.1 (t, J = 7.5 Hz, 2H), 2.4 (m, 2H), 2.1 (br s, m, 4H), 1.2 (t, J = 7.3 Hz, 3H);

MS (APCI) *m/z* 415 $(M + H)^+$.

Part B

3-Chloroperoxybenzoic acid (14.9 g, 66.4 mmol) (mCPBA, available as an approximately 77% pure mixture) was added to a solution of 2-[3-(2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (25.0 g, 60.3 mmol) in chloroform (200 mL), and the reaction was stirred for seven hours at room temperature. An analysis by liquid chromatography/mass spectrometry (LC/MS) indicated that the reaction was incomplete, and additional mCPBA (4.96 g, 22.1 mmol) was added. The reaction was allowed to stir at room temperature overnight. The solution was then washed with brine (2 x 100 mL) and saturated aqueous sodium bicarbonate (2 x 100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a fluffy, light-brown solid. The solid was dried under high vacuum for one hour to provide 25.7 g of 2-[3-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.1 (m, 2H), 8.3 (m, 1H), 7.9-7.7 (m, 6H), 5.0 (t, J = 7.4 Hz, 2H), 4.4 (t, J = 5.3 Hz, 2H), 3.1 (t, J = 7.5 Hz, 2H), 2.4 (m, 2H), 2.1 (br s, m, 4H), 1.2 (t, J = 7.3 Hz, 3H);

MS (APCI) *m/z* 431 $(M + H)^+$.

Part C

Ammonium hydroxide (75 mL) and *p*-toluenesulfonyl chloride (4.87 g, 25.6 mmol) were added to a solution of 2-[3-(5-oxido-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (10.0 g, 23.2 mmol) in

chloroform (100 mL), and the resulting mixture was stirred vigorously for one hour. A white precipitate was removed by filtration, and the filtrate layers were separated. The organic solution was washed with brine (2 x 150 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a yellow solid. The solid was purified by column chromatography on silica gel (eluting with dichloromethane:methanol:ammonium hydroxide ranging in ratios from 94:5:1 to 91:8:1) to provide 4.31 g of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a beige powder, melting point (mp) 145-148 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.1 (d, J = 7.5 Hz, 1H), 7.6 (d, J = 8.3 Hz, 1H), 7.4 (t, J = 8.1 Hz, 1H), 7.3 (t, J = 8.1 Hz, 1H), 6.5 (br s, 2H), 6.1 (br s, 2H), 4.6 (t, J = 7.2 Hz, 2H), 3.6 (t, J = 5.6 Hz, 2H), 2.9 (t, J = 7.4 Hz, 2H), 2.1 (m, 2H), 1.9 (m, 2H), 1.1 (t, J = 7.3 Hz, 3H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 153.4, 152.0, 145.0, 132.6, 126.8, 126.6, 121.5, 120.4, 115.1, 71.6, 42.5, 29.2, 28.5, 21.3, 14.2;

MS (APCI) *m/z* 300 $(M + H)^+$;

Anal. calcd for $C_{16}H_{21}N_5O$: C, 64.19; H, 7.07; N, 23.39. Found: C, 63.94; H, 7.20; N, 23.11.

Part D

Benzaldehyde (383 µL, 3.77 mmol) was added to a mixture of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.800 g, 2.68 mmol) in methanol (15 mL), and the resulting red solution was stirred for two hours. The reaction was then concentrated under reduced pressure, and the residue was purified twice by column chromatography on silica gel (50-60 g, eluting sequentially with 98:2 dichloromethane:methanol and 95:5 dichloromethane:methanol) to provide 0.580 g of (1*E*)-benzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a beige powder, mp 125-128 °C.

^{1}H NMR (300 MHz, $CDCl_3$) 8.1 (s, 1H), 8.0 (d, J = 7.5 Hz, 1H), 7.8 (d, J = 8.3 Hz, 1H), 7.6 (m, 2H), 7.5 (m, 4H), 7.2 (m, 1H), 5.6 (br s, 2H), 4.6 (t, J = 7.5 Hz, 2H), 4.3 (t, J = 5.5 Hz, 2H), 2.9 (t, J = 7.6 Hz, 2H), 2.4 (m, 2H), 1.9 (m, 2H), 1.1 (t, J = 7.4 Hz, 3H);

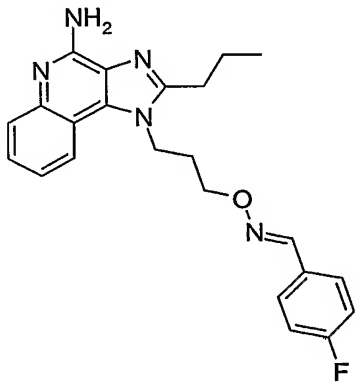
^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 151.2, 149.4, 144.6, 133.2, 131.9, 130.8, 130.2, 128.2, 127.1, 126.9, 122.2, 119.6, 115.4, 70.5, 42.7, 30.0, 29.2, 21.5, 14.0;

MS (APCI) *m/z* 388 $(M + H)^+$;

Anal. calcd for $C_{23}H_{25}N_5O \cdot 0.37H_2O$: C, 70.09; H, 6.58; N, 17.77. Found: C, 69.75; H, 6.60; N, 17.49.

Example 2

(1*E*)-4-Fluorobenzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



4-Fluorobenzaldehyde (307 μL, 2.86 mmol) was added to a mixture of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.800 g, 2.68 mmol) in methanol (15 mL), and the resulting red solution was stirred for two hours. The reaction was then concentrated under reduced pressure, and the residue was purified twice by column chromatography on silica gel (50-60 g, eluting sequentially with 98:2 dichloromethane:methanol and 95:5 dichloromethane:methanol) to provide 600 milligrams (mg) of (1*E*)-4-

fluorobenzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a beige powder, mp 172-175 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (s, 1H), 8.0 (d, J = 8.2 Hz, 1H), 7.8 (d, J = 7.8 Hz, 1H), 7.6 (m, 2H), 7.56 (m, 1H), 7.4 (m, 1H), 7.1 (m, 2H), 5.6 (br s, 2H), 4.6 (t, J = 7.5 Hz, 2H), 4.3 (t, J = 5.5 Hz, 2H), 2.9 (t, J = 7.6 Hz, 2H), 2.4 (m, 2H), 1.9 (m, 2H), 1.1 (t, J = 7.3 Hz, 3H);

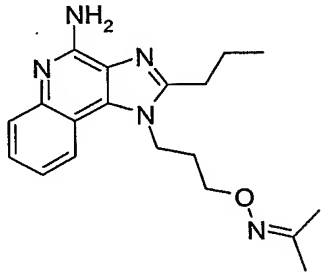
^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9,162.6, 153.7, 151.6, 148.5, 145.7, 145.0, 133.6, 129.4, 129.3, 128.5, 127.5, 127.3, 122.6, 120.0, 116.5, 116.2, 115.8, 70.9, 43.1, 30.3, 29.6, 21.9, 14.4;

MS (APCI) *m/z* 406 $(M + H)^+$;

Anal. calcd for $C_{23}H_{24}FN_5O$: C, 68.13; H, 5.97; N, 17.27. Found: C, 67.82; H, 6.14; N, 16.94.

Example 3

Acetone *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



A mixture of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.605 g, 2.02 mmol) in methanol was heated until the starting material dissolved. Acetone (3 mL, 40 mmol) was then added, and the resulting solution was stirred for two hours. The reaction was then concentrated under reduced pressure, and the residue (800 mg) was purified by column chromatography on silica gel (25 g, eluting sequentially with 98:2 dichloromethane:methanol and 95:5 dichloromethane:methanol) to provide 600 mg of acetone *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a beige powder, mp 147-150 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, J = 8.2 Hz, 1H), 7.8 (d, J = 8.4 Hz, 1H), 7.5 (t, J = 7.1 Hz, 1H), 7.3 (t, J = 8.4 Hz, 1H), 5.6 (br s, 2H), 4.6 (t, J = 7.6 Hz, 2H), 4.2 (t, J = 5.5 Hz, 2H), 2.9 (t, J = 7.6 Hz, 2H), 2.3 (m, 2H), 2.0 (m, 8H), 1.1 (t, J = 7.3 Hz, 3H);

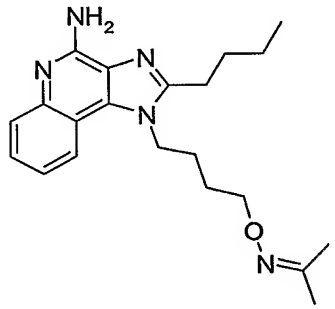
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 153.3, 151.2, 144.7, 133.2, 127.1, 126.9, 122.1, 119.7, 115.5, 69.5, 42.9, 30.0, 29.2, 21.9, 21.6, 15.6, 14.1;

MS (APCI) *m/z* 340 $(M + H)^+$;

Anal. Calcd for $C_{19}H_{25}N_5O \cdot 0.35H_2O$: C, 66.00; H, 7.49; N, 20.26. Found: C, 66.34; H, 7.34; N, 19.88.

Example 4

Acetone *O*-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]oxime



Part A

Triphenylphosphine (21.2 g, 80.7 mmol) and *N*-hydroxyphthalimide (13.2 g, 80.7 mmol) were added to a solution of 4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (16.0 g, 53.8 mmol) in tetrahydrofuran (200 mL). The mixture was stirred for five minutes and then was cooled to approximately 0 °C. Diisopropyl azodicarboxylate (19.6 g, 96.8 mmol) was added dropwise, and the reaction was allowed to warm to room temperature and stirred for three hours. An analysis by LC/MS indicated the presence of starting material, and the reaction was stirred at 60 °C overnight. An analysis by LC/MS indicated the presence of starting material, and additional triphenylphosphine, *N*-hydroxyphthalimide, and diisopropyl azodicarboxylate (26.9 mmol of each) were added to the reaction mixture. The

reaction was stirred at room temperature for two hours and heated at reflux for three hours. The reaction was concentrated under reduced pressure, and the residue was dissolved in chloroform (200 mL). The resulting solution was washed with brine (3 x 150 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure. An analysis of the crude product mixture by LC/MS indicated that starting material was still present. The mixture was dissolved in tetrahydrofuran (200 mL) and treated with triphenylphosphine (21.2 g, 80.7 mmol), *N*-hydroxyphthalimide (13.2 g, 80.7 mmol), and diisopropyl azodicarboxylate (19.6 g, 96.8 mmol) as described above. The reaction was stirred overnight at room temperature. The product was present as a white precipitate, which was isolated by filtration and washed with tetrahydrofuran to provide 8.68 g of 2-[4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.3 (s, 1H), 8.3 (m, 2H), 7.9 (m, 2H), 7.8 (m, 2H), 7.7 (m, 2H), 4.7 (t, J = 7.9 Hz, 2H), 4.3 (t, J = 5.8 Hz, 2H), 3.1 (t, J = 7.6 Hz, 2H), 2.3 (m, 2H), 2.0 (m, 4H), 1.6 (m, 2H), 1.1 (t, J = 7.3 Hz, 3H);
MS (APCI) *m/z* 443 $(M + H)^+$.

Part B

A solution of 2-[4-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione (7.65 g, 17.3 mmol) in dichloromethane (100 mL) was treated with mCPBA (4.65 g, 20.7 mmol), and the resulting orange solution was stirred for four hours at room temperature. The solution was then diluted with dichloromethane (100 ml), washed with brine (3 x 100 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 9.92 g of 2-[4-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione as a red semi-solid.

Part C

A mixture of 2-[4-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione (8.92 g, 19.5 mmol) in dichloroethane (100 mL) was shaken vigorously until it became homogeneous. With vigorous stirring, ammonium hydroxide (100 mL) and *p*-toluenesulfonyl chloride (4.45 g, 23.4 mmol) were added sequentially. The reaction was stirred overnight at room temperature. The product was present as a white precipitate, which was isolated by filtration to provide 1.97 g of 1-[4-(aminooxy)butyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.0 (d, J = 8.2 Hz, 1H), 7.8 (d, J = 8.3 Hz, 1H), 7.5 (t, J = 7.1 Hz, 1H), 7.3 (t, J = 7.1 Hz, 1H), 5.6 (br s, 2H), 5.2 (br s, 2H), 4.5 (t, J = 7.8 Hz, 2H), 3.8 (t, J = 6.2 Hz, 2H), 2.9 (t, J = 7.6 Hz, 2H), 1.7-2.0 (m, 6H), 1.6 (m, 2H), 1.0 (t, J = 7.3 Hz, 3H); MS (APCI) *m/z* 328 $(M + H)^+$.

The filtrate with diluted with chloroform, washed with brine (3 x 100 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 5.72 g additional product as a red semi-solid.

Part D

Acetone (444 mg, 7.65 mmol) was added to a solution of 1-[4-(aminooxy)butyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.500 g, 1.53 mmol) in methanol (7 mL), and the reaction was stirred overnight at room temperature. The solvent was removed under reduced pressure and then further dried under high vacuum to provide 358 mg of acetone *O*-[4-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]oxime as a white solid, mp 115-117 °C.

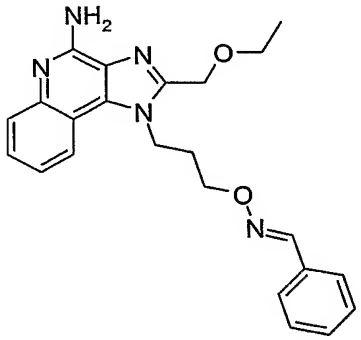
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.0 (d, J = 7.8 Hz, 1H), 7.7 (d, J = 8.3 Hz, 1H), 7.5 (t, J = 8.0 Hz, 1H), 7.3 (t, J = 8.1 Hz, 1H), 6.5 (br s, 2H), 4.5 (t, J = 7.2 Hz, 2H), 4.0 (t, J = 6.0 Hz, 2H), 2.9 (t, J = 7.5 Hz, 2H), 1.9-1.6 (m, 12H), 1.5 (m, 2H), 1.1 (t, J = 7.3 Hz, 3H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 154.2, 153.4, 152.0, 144.8, 132.6, 128.4, 126.6, 126.4, 121.5, 120.3, 115.1, 71.9, 44.9, 30.0, 26.8, 26.5, 25.9, 22.3, 21.6, 15.4, 14.1;
MS (APCI) *m/z* 368 $(M + H)^+$;
HRMS (ESI) Theoretical mass: 368.2469, measured mass: 368.2450.

For Examples 5, 6, and 7 the final compounds were purified by flash chromatography using a 10 g silica gel cartridge (RediSep, ISCO, 230-400 mesh) attached to a gradient pump system, 254 nanometers (nm) UV detector, and fraction collector (ISCO COMBIFLASH Sg100c system). The column was equilibrated with dichloromethane:methanol with or without approximately 1% ammonium hydroxide, and the reaction mixture was injected onto the column. The mixture was eluted with a gradient program using a solvent system consisting of dichloromethane:methanol with or without approximately 1% ammonium hydroxide. The gradient started with a lower percentage of methanol (approximately 1%) and the percentage of methanol was gradually increased (to up to approximately 10%) to elute the desired compound. Fractions were examined by thin layer chromatography and by LC/MS and those containing the desired compound were combined and concentrated.

Example 5

(1*E*)-Benzaldehyde *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime



Part A

Triphenylphosphine (8.71 g, 33.2 mmol) and *N*-hydroxyphthalimide (5.42 g, 33.2 mmol) were added to a solution of 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propan-1-ol (6.31 g, 22.1 mmol) in tetrahydrofuran (150 mL). The reaction was stirred under nitrogen and cooled to approximately 0°C. Diisopropyl azodicarboxylate (17.5 mL, 89.1 mmol) was then added dropwise over a period of 15 minutes. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (200 mL). The solution was extracted with 6 normal (N) hydrochloric acid (3 x 200 mL), and sodium hydroxide pellets were added to the combined extracts until the solution was basic. The aqueous solution was then extracted with chloroform (4 x), and the combined extracts were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and concentrated under reduced pressure to provide 4 g of 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline.

Part B

Benzaldehyde (340 µL, 3.3 mmol) was added to a solution of 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.00 g, 3.33 mmol) in methanol (4 mL), and the resulting solution was stirred overnight at room

temperature. The methanol was removed under reduced pressure to provide 1.42 g of (1*E*)-benzaldehyde *O*-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime, which was used without purification.

Part C

The material from Part B was dissolved in dichloromethane (5 mL), and mCPBA (984 mg, 4.39 mmol) was added. The reaction was stirred for one hour and then diluted with dichloromethane. The solution was washed with saturated aqueous sodium bicarbonate (2 x 50 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, concentrated under reduced pressure, and further dried under high vacuum to provide 1.03 g of (1*E*)-benzaldehyde *O*-{3-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime as a red, glassy solid.

Part D

Ammonium hydroxide (15 mL) was added with vigorous stirring to a solution of (1*E*)-benzaldehyde *O*-{3-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime (1.03 g, 2.55 mmol) in dichloroethane (15 mL). *p*-Toluenesulfonyl chloride (572 mg), 3.00 mmol) was added, and the reaction was stirred for two hours at room temperature. The reaction was diluted with dichloromethane, and the organic solution was washed with brine (2 x 50 mL), dried over magnesium sulfate, filtered through a layer of CELITE filter aid, concentrated under reduced pressure, and further dried under high vacuum to provide a brown and white solid. The solid was purified by flash chromatography using the method described above to provide 296 mg of (1*E*)-benzaldehyde *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime as a brown powder, mp 133-135 °C.

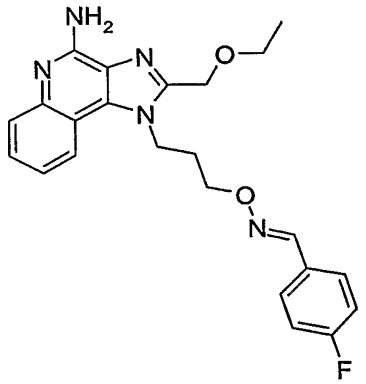
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.4 (s, 1H), 8.1 (d, J = 7.9 Hz, 1H), 7.7 (m, 3H), 7.5 (m, 4H), 7.2 (t, J = 7.1 Hz, 1H), 6.7 (br s, 2H), 4.8 (m, 4H), 4.4 (t, J = 5.6 Hz, 2H), 3.7 (q, J = 7.0 Hz, 2H), 2.3 (m, 2H), 1.2 (t, J = 6.8 Hz, 3H);

MS (APCI) *m/z* 404 $(M + H)^+$;

Anal. calcd for $C_{23}H_{25}N_5O_2$: C, 68.47; H, 6.25; N, 17.36. Found: C, 68.18; H, 6.08; N, 17.07.

Example 6

(1*E*)-4-Fluorobenzaldehyde *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime



Part A

4-Fluorobenzaldehyde (357 μL, 3.37 mmol) was added to a solution of 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.00 g, 3.33 mmol), prepared in Part A of Example 5, in methanol (4 mL), and the resulting solution was stirred overnight at room temperature. The methanol was removed under reduced pressure to provide 1.29 g of (1*E*)-4-fluorobenzaldehyde *O*-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime, which was used without purification.

Part B

The general method described in Part C of Example 5 was used to oxidize (1*E*)-4-fluorobenzaldehyde *O*-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime (1.29 g, 3.18 mmol) with mCPBA (855 mg, 3.81 mmol) to provide 851 mg of (1*E*)-4-fluorobenzaldehyde *O*-{3-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime as a red, tarry solid.

Part C

The general method described in Part D of Example 5 was used to aminate (1*E*)-4-fluorobenzaldehyde *O*-{3-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime (851 mg, 2.02 mmol). (1*E*)-4-Fluorobenzaldehyde *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime (346 mg) was obtained as a beige powder, mp 157-158 °C.

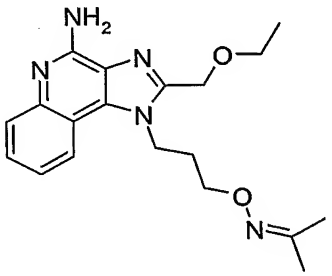
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.4 (s, 1H), 8.1 (d, J = 7.5 Hz, 1H), 7.7 (m, 2H), 7.6 (d, J = 8.4 Hz, 1H), 7.4 (t, J = 7.1 Hz, 1H), 7.3 (m, 2H), 7.1 (t, J = 8.2 Hz, 1H), 6.7 (br s, 2H), 4.8 (m, 4H), 4.3 (t, J = 5.6 Hz, 2H), 3.6 (q, J = 7.0 Hz, 2H), 2.3 (m, 2H), 1.2 (t, J = 7.0 Hz, 3H);

MS (APCI) *m/z* 422 $(M + H)^+$;

Anal. calcd for $C_{23}H_{24}FN_5O_2$: C, 65.54; H, 5.74; N, 16.62. Found: C, 65.32; H, 5.81; N, 16.46.

Example 7

Acetone *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime



Part A

Acetone (193 mg, 3.33 mmol) was added to a solution of 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinoline (1.00 g, 3.33 mmol), prepared in Part A of Example 5, in methanol (4 mL), and the resulting solution was stirred overnight at room temperature. The methanol was removed

under reduced pressure to provide 1.06 g of acetone *O*-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime, which was used without purification.

Part B

The general method described in Part C of Example 5 was used to oxidize acetone *O*-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime (1.06 g, 3.12 mmol) with mCPBA (838 mg, 3.74 mmol) to provide 729 mg of acetone *O*-{3-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime as a red solid.

Part C

The general method described in Part D of Example 5 was used to aminate acetone *O*-{3-[2-(ethoxymethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime (726 mg, 2.04 mmol). Acetone *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]propyl}oxime (136 mg) was obtained as an off-white crystalline solid, mp 109-111 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (d, J = 8.2 Hz, 1H), 7.8 (d, J = 8.4 Hz, 1H), 7.5 (t, J = 7.1 Hz, 1H), 7.3 (t, J = 7.1 Hz, 1H), 5.6 (br s, 2H), 4.8 (s, 2H), 4.75 (t, J = 6.1 Hz, 2H), 4.2 (t, J = 5.5 Hz, 2H), 3.6 (q, J = 7.0 Hz, 2H), 2.4 (m, 2H), 2.0 (s, 3H), 1.9 (s, 3H), 1.3 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 151.8, 149.5, 145.4, 134.5, 127.7, 127.5, 127.1, 122.7, 120.5, 115.8, 70.3, 66.6, 65.5, 44.1, 30.4, 22.3, 16.0, 15.5;

MS (APCI) *m/z* 356 $(M + H)^+$;

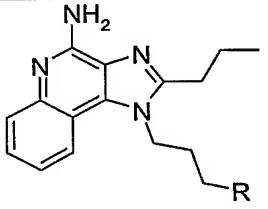
Anal. calcd for $C_{19}H_{25}N_5O_2$: C, 64.20; H, 7.09; N, 19.70. Found: C, 63.98; H, 7.22; N, 19.40.

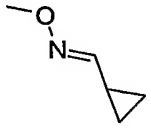
Examples 8-83

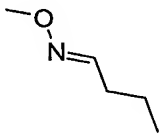
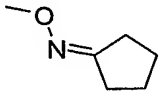
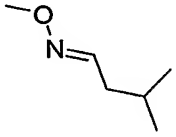
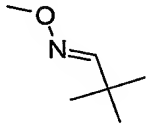
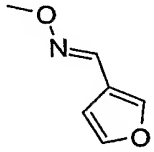
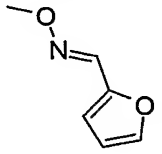
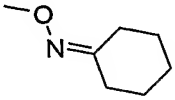
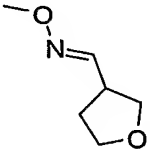
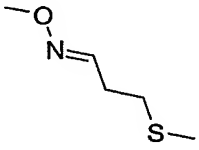
An aldehyde or ketone from the table below (1.1 equivalents, 0.071 mmol) was added to a test tube containing a solution of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (20 mg, 0.066 mmol) in methanol (1 mL). The

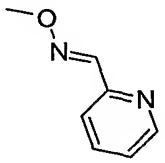
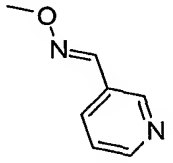
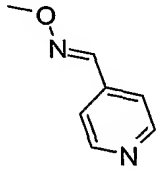
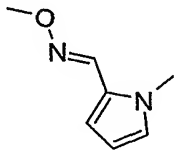
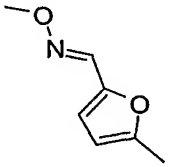
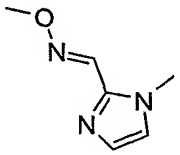
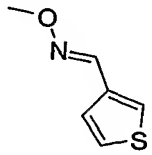
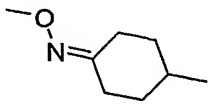
test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC-TOFMS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Phenomenex LUNA C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size, 100 Angstroms (Å) pore; flow rate: 25 mL/min; non-linear gradient elution from 5-95% B in 9 min, then hold at 95% B for 2 min, where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the ketone or aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

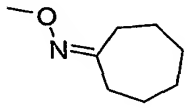
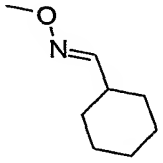
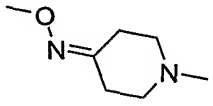
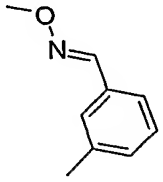
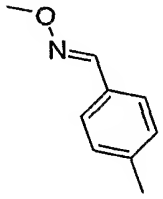
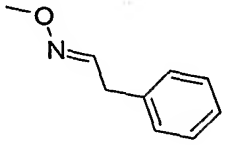
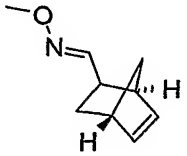
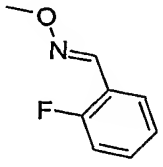
Examples 8-83

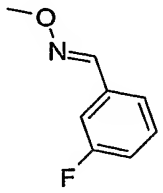
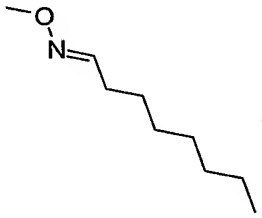
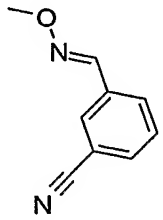
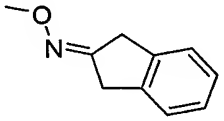
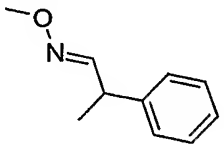
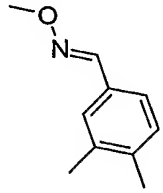
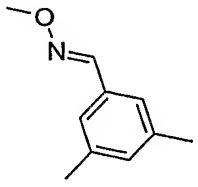


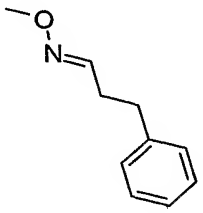
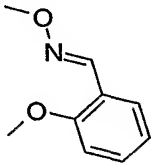
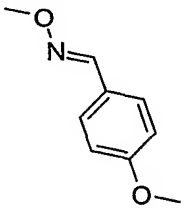
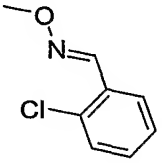
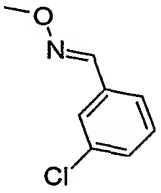
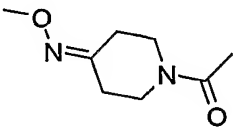
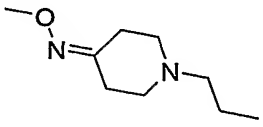
Ex.	Aldehyde or Ketone	R	Measured Mass (M+H)
8	Cyclopropane-carboxaldehyde		352.2163

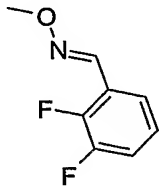
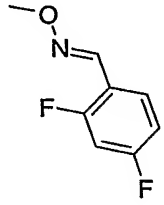
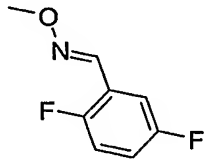
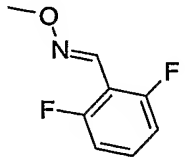
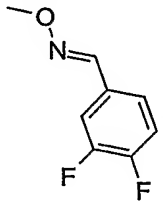
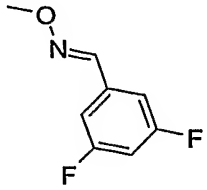
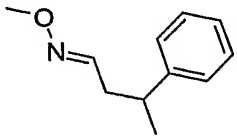
9	Butyraldehyde		354.2321
10	Cyclopentanone		366.2313
11	Isovaleraldehyde		368.2447
12	Trimethylacetaldehyde		368.2451
13	3-Furaldehyde		378.1914
14	Furfural		378.1929
15	Cyclohexanone		380.2452
16	Tetrahydrofuran-3-carboxaldehyde (50% in water)		382.2266
17	3-(Methylthio) propionaldehyde		386.2041

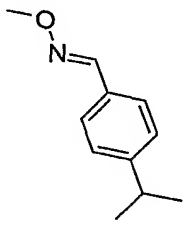
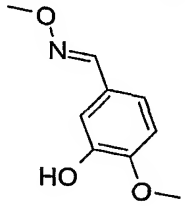
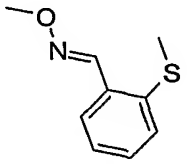
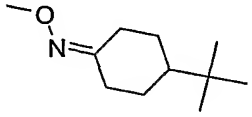
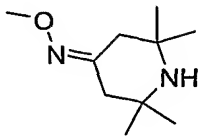
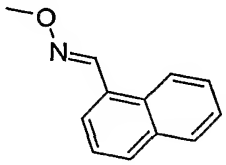
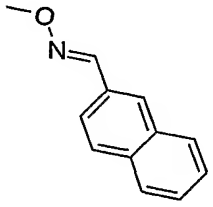
18	2-Pyridinecarboxaldehyde		389.2112
19	3-Pyridinecarboxaldehyde		389.2113
20	4-Pyridinecarboxaldehyde		389.2090
21	1-Methylpyrrole-2-carboxaldehyde		391.2253
22	5-Methylfurfural		392.2091
23	1-Methyl-2-imidazolecarboxaldehyde		392.2209
24	3-Thiophenecarboxaldehyde		394.1690
25	4-Methylcyclohexanone		394.2638

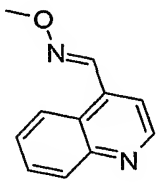
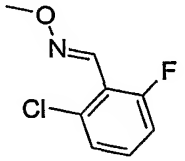
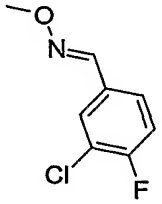
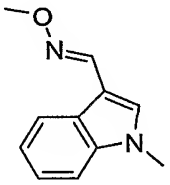
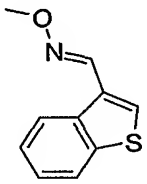
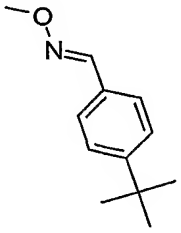
26	Cycloheptanone		394.2619
27	Cyclohexanecarboxaldehyde		394.2636
28	1-Methyl-4-piperidone		395.2582
29	*m*-Tolualdehyde		402.2304
30	*p*-Tolualdehyde		402.2317
31	Phenylacetaldehyde		402.2297
32	5-Norbornene-2-carboxaldehyde		404.2444
33	2-Fluorobenzaldehyde		406.2079

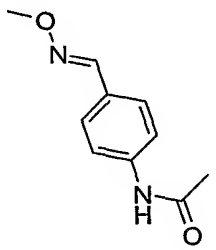
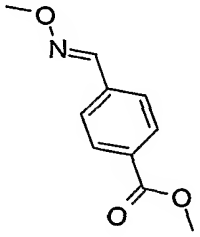
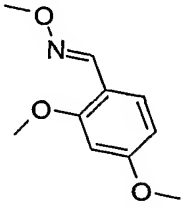
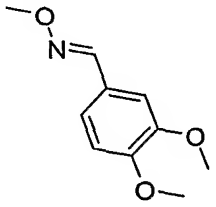
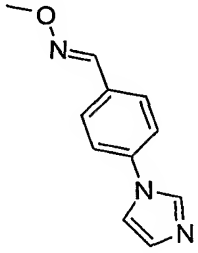
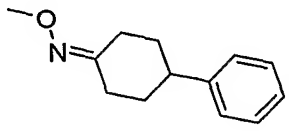
34	3-Fluorobenzaldehyde		406.2060
35	Octanal		410.2934
36	3-Cyanobenzaldehyde		413.2113
37	2-Indanone		414.2309
38	2-Phenylpropionaldehyde		416.2444
39	3,4-Dimethylbenzaldehyde		416.2476
40	3,5-Dimethylbenzaldehyde		416.2473

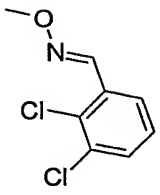
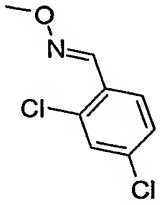
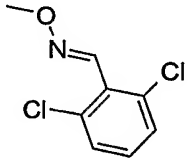
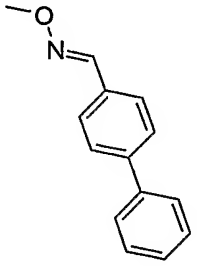
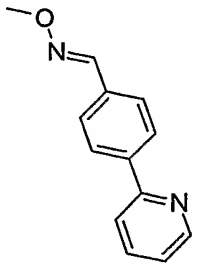
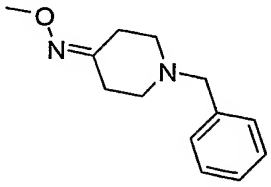
41	3-Phenylpropionaldehyde		416.2482
42	2-Methoxybenzaldehyde		418.2265
43	*p*-Anisaldehyde		418.2257
44	2-Chlorobenzaldehyde		422.1773
45	3-Chlorobenzaldehyde		422.1741
46	1-Acetyl-4-piperidone		423.2539
47	1-Propyl-4-piperidone		423.2877

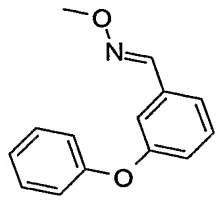
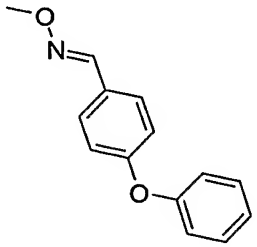
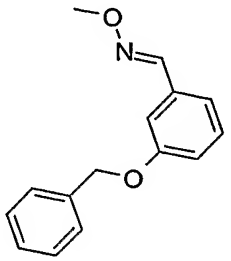
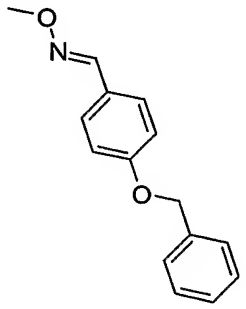
48	2,3-Difluorobenzaldehyde		424.1971
49	2,4-Difluorobenzaldehyde		424.1985
50	2,5-Difluorobenzaldehyde		424.1946
51	2,6-Difluorobenzaldehyde		424.1976
52	3,4-Difluorobenzaldehyde		424.1960
53	3,5-Difluorobenzaldehyde		424.1975
54	3-Phenylbutyraldehyde		430.2623

55	Cuminaldehyde		430.2630
56	3-Hydroxy-4-Methoxybenzaldehyde		434.2180
57	2-(Methylthio)benzaldehyde		434.2025
58	4-*tert*-Butylcyclohexanone		436.3089
59	2,2,6,6-Tetramethyl-4-piperidone		437.3042
60	1-Naphthaldehyde		438.2296
61	2-Naphthaldehyde		438.2321

62	4-Quinolinecarboxaldehyde		439.2276
63	2-Chloro-6-fluorobenzaldehyde		440.1650
64	3-Chloro-4-fluorobenzaldehyde		440.1657
65	1-Methylindole-3-carboxaldehyde		441.2405
66	Thianaphthene-3-carboxaldehyde		444.1878
67	4-*tert*-Butylbenzaldehyde		444.2747

68	4-Acetamidobenzaldehyde		445.2375
69	Methyl 4-formylbenzoate		446.2195
70	2,4-Dimethoxybenzaldehyde		448.2351
71	3,4-Dimethoxybenzaldehyde		448.2359
72	4-(1*H*-Imidazol-1-yl)benzaldehyde		454.2388
73	4-Phenylcyclohexanone		456.2742

74	2,3-Dichlorobenzaldehyde		456.1371
75	2,4-Dichlorobenzaldehyde		456.1389
76	2,6-Dichlorobenzaldehyde		456.1345
77	4-Biphenylcarboxaldehyde		464.2472
78	4-(2-Pyridyl)benzaldehyde		465.2433
79	1-Benzyl-4-piperidone		471.2900

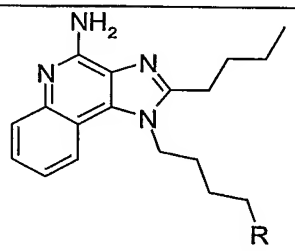
80	3-Phenoxybenzaldehyde		480.2427
81	4-Phenoxybenzaldehyde		480.2393
82	3-Benzyloxybenzaldehyde		494.2564
83	4-Benzyloxybenzaldehyde		494.2585

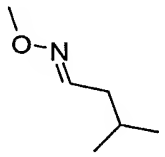
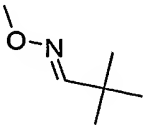
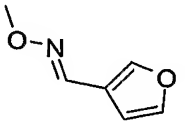
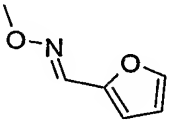
Examples 84-126

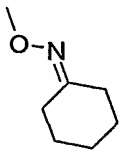
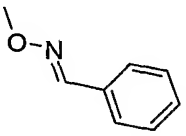
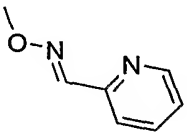
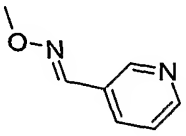
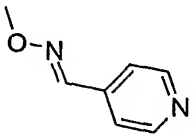
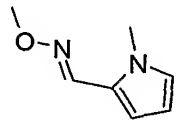
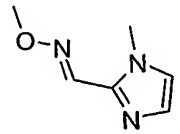
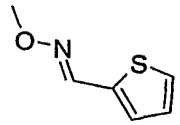
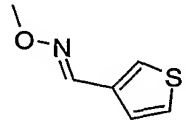
An aldehyde or ketone from the table below (1.1 equivalents, 0.11 mmol) was added to a test tube containing a solution of 1-[4-(aminooxy)butyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (32 mg, 0.098 mmol) in methanol (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (~18 hours). The solvent was removed by vacuum centrifugation. The compounds were

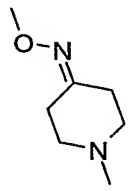
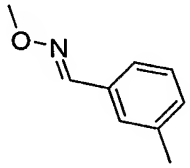
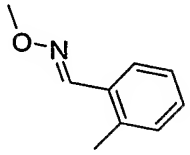
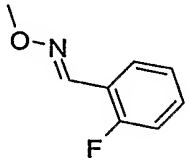
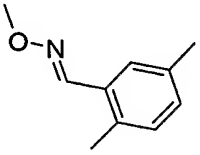
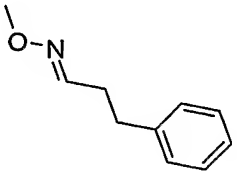
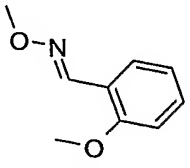
purified as described for Examples 8-83. The table below shows the ketone or aldehyde used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

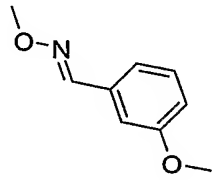
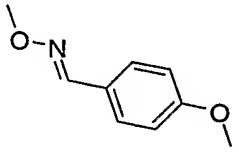
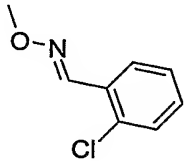
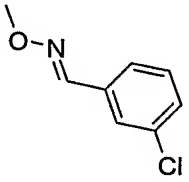
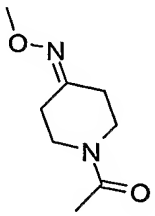
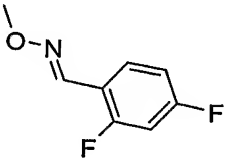
Examples 84-126

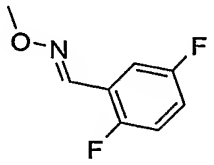
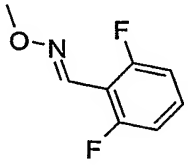
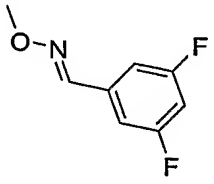
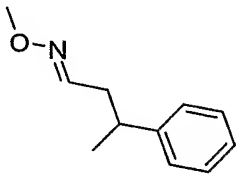
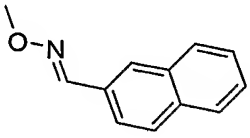
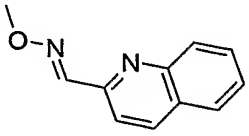
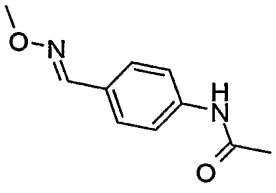


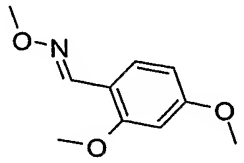
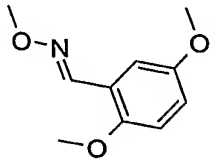
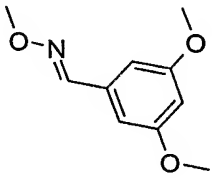
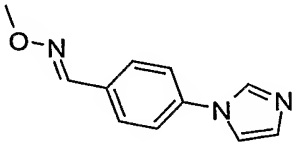
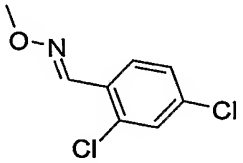
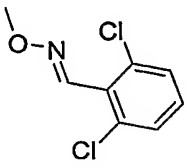
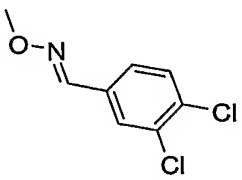
Ex.	Aldehyde or Ketone	R	Measured Mass (M+H)
84	Isovaleraldehyde		396.2747
85	Trimethylacetaldehyde		396.2743
86	3-Furaldehyde		406.2266
87	Furfural		406.2257

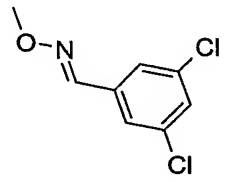
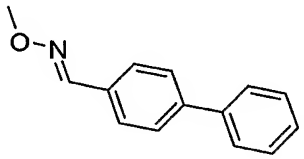
88	Cyclohexanone		408.2744
89	Benzaldehyde		416.2440
90	2-Pyridinecarboxaldehyde		417.2394
91	3-Pyridinecarboxaldehyde		417.2365
92	4-Pyridinecarboxaldehyde		417.2430
93	1-Methylpyrrole-2-carboxaldehyde		419.2578
94	1-Methyl-2-imidazolecarboxaldehyde		420.2485
95	2-Thiophenecarboxaldehyde		422.2002
96	3-Thiophenecarboxaldehyde		422.2031

97	1-Methyl-4-piperidone		423.2871
98	*m*-Tolualdehyde		430.2621
99	*o*-Tolualdehyde		430.2603
100	2-Fluorobenzaldehyde		434.2378
101	2,5-Dimethylbenzaldehyde		444.2778
102	3-Phenylpropionaldehyde		444.2782
103	2-Methoxybenzaldehyde		446.2560

104	3-Methoxybenzaldehyde		446.2574
105	*p*-Anisaldehyde		446.2578
106	2-Chlorobenzaldehyde		450.2086
107	3-Chlorobenzaldehyde		450.2083
108	1-Acetyl-4-piperidone		451.2798
109	2,3-Difluorobenzaldehyde		452.2256
110	2,4-Difluorobenzaldehyde		452.2295

111	2,5-Difluorobenzaldehyde		452.2298
112	2,6-Difluorobenzaldehyde		452.2282
113	3,5-Difluorobenzaldehyde		452.2297
114	3-Phenylbutyraldehyde		458.2908
115	2-Naphthaldehyde		466.2631
116	2-Quinolinecarboxaldehyde		467.2558
117	4-Acetamidobenzaldehyde		473.2665

118	2,4-Dimethoxybenzaldehyde		476.2665
119	2,5-Dimethoxybenzaldehyde		476.2667
120	3,5-Dimethoxybenzaldehyde		476.2677
121	4-(1*H*-Imidazol-1-yl)benzaldehyde		482.2682
122	2,4-Dichlorobenzaldehyde		484.1685
123	2,6-Dichlorobenzaldehyde		484.1673
124	3,4-Dichlorobenzaldehyde		484.1673

125	3,5-Dichlorobenzaldehyde		484.1679
126	4-Biphenylcarboxaldehyde		492.2738

Examples 127-135

Part A

To a solution of 4-chloro-3-nitro[1,5]naphthyridine (18.0 g, 85.9 mmol) in dichloromethane (220 mL) at room temperature was added triethylamine (15.6 mL, 112 mmol) and 3-amino-1-propanol (7.20 mL, 94.5 mmol). The solution was stirred for 4 hours, then was concentrated under reduced pressure to yield an orange solid. The solid was slurried in water (250 mL) for 30 minutes, isolated by filtration, washed with water (3 x 30 mL), and dried at 70 °C in a vacuum oven to afford 20.9 g of 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propan-1-ol as a yellow solid.

Part B

Acetic anhydride (7.30 mL, 77.3 mmol) was added slowly to a 0 °C solution of 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propan-1-ol (16.0 g, 64.5 mmol), 4-dimethylaminopyridine (0.39 g, 3.2 mmol), and triethylamine (12.6 mL, 90.2 mmol) in dichloromethane (250 mL). The solution was stirred at 0 °C for 45 minutes, then was diluted with dichloromethane (50 mL) and washed with saturated aqueous sodium bicarbonate (150 mL). The aqueous layer was extracted with dichloromethane (2 x 40 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford

19.74 g of 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propyl acetate as a yellow solid, which contained a trace amount of triethylamine and acetic acid and was used without purification.

Part C

A mixture of the 3-[(3-nitro[1,5]naphthyridin-4-yl)amino]propyl acetate (12.00 g, 41.3 mmol) and 5% platinum on carbon (1.2 g) in ethyl acetate (125 mL) was hydrogenated at 30 psi (2.1×10^5 Pa) on a Parr apparatus for 3 hours. The mixture was filtered through CELITE filter agent, which was rinsed with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure to 12.7 g of 3-[(3-amino[1,5]naphthyridin-4-yl)amino]propyl acetate as a golden oil.

Part D

Butyryl chloride (4.7 mL, 45.4 mmol) was added dropwise to a solution of material from Part C in dichloromethane (160 mL) at 0 °C. The solution was allowed to warm to room temperature and stir for 1 hour, then was concentrated under reduced pressure to provide 3-{[3-(butyrylamino)[1,5]naphthyridin-4-yl]amino}propyl acetate hydrochloride as a dark orange foam that was used directly in the next step.

Part E

To the material from Part D was added ethanol (165 mL) and 2 M sodium hydroxide (62.0 mL, 124 mmol). The resulting solution was heated at 60 °C for 7 hours, then was stirred at room temperature overnight. The solution was concentrated under reduced pressure and the resulting residue was dissolved in dichloromethane (250 mL) and washed with water (125 mL). The aqueous layer was extracted with dichloromethane (75 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 9.24 g of 3-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propan-1-ol as a brown oil.

Part F

Diisopropyl azodicarboxylate (8.10 mL, 48.4 mmol) was added dropwise over ten minutes to a stirred solution of 3-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propan-1-ol (10.9 g, 40.3 mmol), triphenylphosphine (12.7 g, 48.4 mmol), and *N*-hydroxyphthalimide (7.89 g, 48.4 mmol) in tetrahydrofuran (160 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. The solvent was removed under reduced pressure to afford an oil that was dissolved in ethyl acetate (200 mL) and extracted with 2 M HCl (3 x 100 mL). The aqueous layers were combined, and the pH was adjusted to 7 with the addition of solid sodium bicarbonate. A precipitate formed, was isolated by filtration, and was dissolved in dichloromethane (300 mL). The solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 17.38 g of 2-[3-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione as a tan solid.

Part G

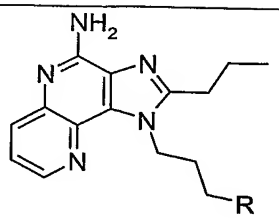
To a solution of 2-[3-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (6.00 g, 14.4 mmol) in chloroform (70 mL) at room temperature was added mCPBA (3.37 g, 19.5 mmol). The reaction was stirred for 5 hours and then concentrated ammonium hydroxide (40 mL) was added followed by portionwise addition of *p*-toluenesulfonyl chloride (3.03 g, 15.9 mmol). The mixture was stirred overnight and then was filtered to afford 3.99 g of crude product. The filtrate was diluted with brine (50 mL) and extracted with dichloromethane (2 x 20 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford an orange solid, which was triturated with methanol and isolated by filtration to provide an additional 0.450 g of product. The product was combined and purified by chromatography on a HORIZON HPFC system (an automated, modular high-performance flash purification product available from Biotage, Inc, Charlottesville,

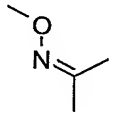
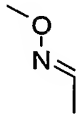
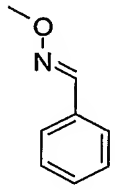
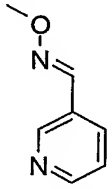
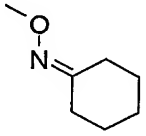
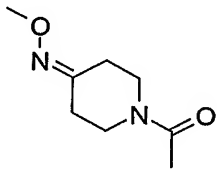
Virginia, USA) (silica gel, gradient elution with 0-35% CMA in chloroform where CMA is 80:18:2 chloroform/methanol/concentrated ammonium hydroxide) to afford 2.23 g of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a pale yellow solid.

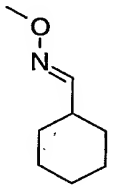
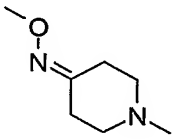
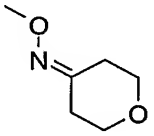
Part H

For the synthesis of Examples 127-135, the following procedure was used: to a 0.2 M suspension of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (typically 0.9-3 mmol) in methanol at room temperature was added a ketone or an aldehyde from the table below. The equivalents of ketone or aldehyde used relative to the amount of 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine are shown in the table. The reaction mixture was stirred at room temperature for the length of time indicated in the table. In all cases except Example 127, a solution formed that was concentrated under reduced pressure. The resulting residue was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with CMA in chloroform). The solid obtained after chromatography was concentrated from acetonitrile (Examples 128, 129, and 131), or triturated with acetonitrile (Example 130), or recrystallized from ethyl acetate/hexanes (Example 132) or from dichloromethane/hexanes (Example 133). In Example 127, the reaction mixture was filtered directly to yield crude product, which was subsequently purified by trituration with methanol and then concentrated from ethyl acetate. In all cases, the final material was dried at elevated temperature under vacuum to yield the Examples listed in Table 1. Example 128 was isolated as a 70:30 mixture of *E*:*Z* isomers.

Table 1



Example	Ketone or Aldehyde	R	Equivalents	Reaction Time
127	Acetone		13.6	3 days
128	Acetaldehyde		5.0	2 hours
129	Benzaldehyde		1.3	4 hours
130	3-Pyridinecarboxaldehyde		1.2	18 hours
131	Cyclohexanone		1.2	1 hour
132	N-Acetyl-4-piperidone		1.2	2.5 hours

133	Cyclohexanecarboxaldehyde		1.2	18 hours
134	N-Methyl-4-piperidone		1.1	18 hours
135	Tetrahydro-4*H*-pyran-4-one		1.05	18 hours

The characterization data for Examples 127-135 are shown in the table below.

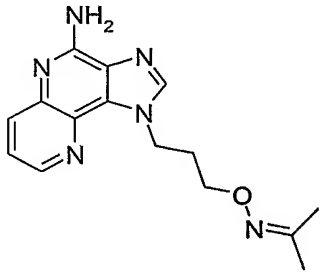
Example	Name	Form, Mp (°C)	Elemental Analysis
127	Acetone *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	off-white crystals, 160-162	Anal. calcd for $C_{18}H_{24}N_6O$: C, 63.51; H, 7.11; N, 24.69. Found: C, 63.26; H, 7.40; N, 24.61
128	(1*E*)-Ethanal *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	off-white needles, 140-143	Anal. calcd for $C_{17}H_{22}N_6O$: C, 62.56; H, 6.79; N, 25.75. Found: C, 62.28; H, 6.93; N, 25.86

129	(1*E*)-Benzaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	beige needles, 112-114	Anal. calcd for $C_{22}H_{24}N_6O$: C, 68.02; H, 6.23; N, 21.63. Found: C, 67.76; H, 6.29; N, 21.78
130	(1*E*)-Nicotinaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	off-white needles, 152-154	Anal. calcd for $C_{21}H_{23}N_7O$: C, 64.76; H, 5.95; N, 25.18. Found: C, 64.43; H, 6.11; N, 25.46
131	Cyclohexanone *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	off-white needles, 138-140	Anal. calcd for $C_{21}H_{28}N_6O$: C, 66.29; H, 7.42; N, 22.09. Found: C, 66.00; H, 7.68; N, 22.19
132	1-Acetylpiperidin-4-one *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	beige needles, 164-165	Anal. calcd for $C_{22}H_{29}N_7O_2$: C, 62.39; H, 6.90; N, 23.15. Found: C, 62.09; H, 7.09; N, 23.26
133	(1*E*)-Cyclohexanecarbaldehyde *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	beige needles, 123-124	Anal. calcd for $C_{22}H_{30}N_6O$: C, 66.98; H, 7.66; N, 21.30. Found: C, 66.87; H, 7.85; N, 21.36

134	1-Methylpiperidin-4-one *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	yellow needles, 126-127	Anal. calcd for $C_{21}H_{29}N_7O$: C, 63.77; H, 7.39; N, 24.79. Found: C, 63.50; H, 7.39; N, 24.76
135	Tetrahydro-4*H*-pyran-4-one *O*-[3-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*]-1,5-naphthyridin-1-yl)propyl]oxime	beige needles, 166-167	Anal. calcd for $C_{20}H_{26}N_6O_2$: C, 62.81; H, 6.85; N, 21.97. Found: C, 62.61; H, 7.04; N, 21.94

Example 136

Acetone *O*-[3-(4-amino-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propyl]oxime



Part A

Triethyl orthoformate (1.86 mL, 17.0 mmol) and pyridine hydrochloride (0.164 g, 1.42 mmol) were added to a stirred suspension of 3-[(3-amino[1,5]naphthyridin-4-yl)amino]propyl acetate (prepared as described in Part C of Examples 127-135, 3.70 g, 14.2 mmol) in toluene (70 mL). The mixture was heated at reflux with a Dean-Stark trap. After 2.5 hours, additional triethyl orthoformate (1 mL) was added and heating was continued for another 2 hours. The mixture was allowed to cool to room temperature and was concentrated under reduced pressure to afford a dark oil that was dissolved in dichloromethane (100 mL). The solution was washed with saturated aqueous sodium bicarbonate (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to

afford 3.50 g of 3-(1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propyl acetate as an orange oil that was used without further purification in the next step.

Part B

Solid potassium carbonate (2.68 g, 19.4 mmol) was added to a solution of 3-(1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propyl acetate (3.50 g, 12.9 mmol) in methanol (65 mL) at room temperature. The mixture was stirred for 3 hours, then the solvent was removed under reduced pressure. The residue was partitioned between dichloromethane (150 mL) and water (75 mL). The organic layer was washed with brine (75 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a brown semi-solid that was triturated with dichloromethane and isolated by filtration to afford 0.48 g of 3-(1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propan-1-ol. The filtrate was concentrated under reduced pressure, and the residue was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-50% CMA in chloroform) to provide an additional 0.67 g of 3-(1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propan-1-ol.

Part C

Diisopropyl azodicarboxylate (1.01 mL, 6.05 mmol) was added dropwise to a stirred solution of 3-(1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propan-1-ol (1.15 g, 5.04 mmol), triphenylphosphine (1.59 g, 6.05 mmol), and *N*-hydroxyphthalimide (0.986 g, 6.05 mmol) in tetrahydrofuran (25 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. The product was isolated by filtration and washed with a minimal amount of tetrahydrofuran to afford 1.47 g of 2-[3-(1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione as a pale yellow solid.

Part D

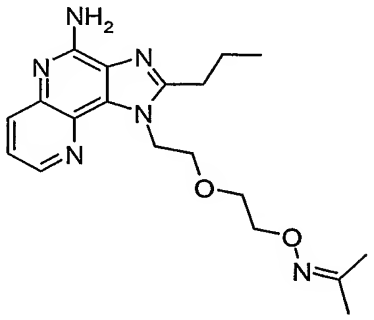
A modification of the procedure described in Part G of Examples 127-135 was used to convert 2-[3-(1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (1.47 g, 3.94 mmol) into 0.237 g of 1-[3-(aminooxy)propyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. In this case, the solid isolated from the crude reaction mixture was not the desired product. The filtrate was diluted with saturated aqueous sodium bicarbonate (50 mL) and extracted with chloroform (2 x 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to an oil that was purified by chromatography on a HORIZON HPFC system (0-50% CMA in chloroform) to afford 0.237 g of 1-[3-(aminooxy)propyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

Part E

Acetone (1 mL) was added to a suspension of 1-[3-(aminooxy)propyl]-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.237 g, 0.92 mmol) in methanol (6 mL) at room temperature. The mixture was stirred and eventually a solution formed. After 6 hours, the volatiles were removed and the crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-25% CMA in chloroform) to give a white powder that was crystallized from acetonitrile to yield 0.110 g of acetone *O*-[3-(4-amino-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)propyl]oxime as white needles, mp 120-121 °C.
MS (APCI) *m/z* 299 $(M + H)^+$;
Anal. calcd for $C_{15}H_{18}N_6O$: C, 60.39; H, 6.08; N, 28.17. Found: C, 60.34; H, 6.21; N, 28.37.

Example 137

Acetone *O*-{2-[2-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethyl}oxime



Part A

Following the general procedures described in Parts A-D of Examples 127-135, 4-chloro-3-nitro[1,5]naphthyridine (5.29 g, 25.2 mmol) was converted into 2-(2-{[3-(butyrylamino)[1,5]naphthyridin-4-yl]amino}ethoxy)ethyl acetate hydrochloride (approximately 24.5 mmol) using 2-(2-aminoethoxy)ethanol (2.8 mL, 27.8 mmol) in lieu of 3-amino-1-butanol in Part A of Examples 127-135.

Part B

Modifying the procedure described in Part E of Examples 127-135, 2-(2-{[3-(butyrylamino)[1,5]naphthyridin-4-yl]amino}ethoxy)ethyl acetate hydrochloride (approximately 24.5 mmol) was treated with 2 M NaOH (37 mL, 73.5 mmol) in ethanol. After the solution was heated at 60 °C overnight, more 2 M NaOH was added (1 equivalent) and the mixture was heated at 70 °C for 8 hours. After the work-up described in Part E of Examples 127-135, 6.55 g of 2-[2-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethanol was isolated as an orange solid.

Part C

Following the general procedure described in Part F of Examples 127-135, 2-[2-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethanol (6.50 g,

21.6 mmol) was converted into 2-{2-[2-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione. After the work-up described in Part F of Examples 127-135, the resulting oil was triturated with acetonitrile (60 mL) and a solid was isolated by filtration and dried to provide 7.76 g of 2-{2-[2-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione as a pale yellow solid.

Part D

Following the general procedure described in Part D of Example 136, 2-{2-[2-(2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione (7.76 g, 18.7 mmol) was converted into 1-{2-[2-(aminooxy)ethoxy]ethyl}-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. In this case, purification by chromatography was unnecessary and the crude product was triturated with acetonitrile to afford 2.71 g of 1-{2-[2-(aminooxy)ethoxy]ethyl}-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

Part E

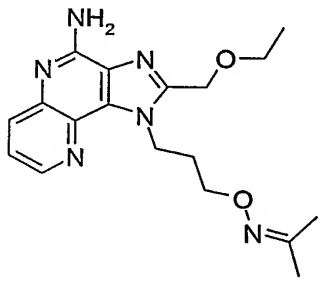
Following the general procedure described in Part E of Example 136, 1-{2-[2-(aminooxy)ethoxy]ethyl}-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.510 g, 1.54 mmol) was converted into acetone *O*-{2-[2-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethyl}oxime. After purification of the crude product by chromatography on a HORIZON HPFC system, the resulting white solid was triturated with acetonitrile and dried under vacuum to provide 0.229 g of acetone *O*-{2-[2-(4-amino-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl)ethoxy]ethyl}oxime as white needles, mp 127-128 °C.

MS (APCI) *m/z* 371 $(M + H)^+$;

Anal. calcd for $C_{19}H_{26}N_6O_2$: C, 61.60; H, 7.07; N, 22.69. Found: C, 61.60; H, 7.25; N, 22.77.

Example 138

Acetone *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime



Part A

Following the general procedures described in Parts D and E of Examples 127-135, 3-[(3-amino[1,5]naphthyridin-4-yl)amino]propyl acetate (prepared as described in Parts A-C of Examples 127-135, approximately 14.6 mmol) was converted into 3.18 g of 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propan-1-ol using ethoxyacetyl chloride in lieu of butyryl chloride in Part D of Examples 127-135.

Part B

Following the general procedure described in Part F of Examples 127-135, 3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propan-1-ol (3.18 g, 11.1 mmol) was converted into 2-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione. During the extraction with 2 N HCl, a solid formed which was isolated, washed with water, and dried. The solid was dissolved in dichloromethane (150 mL) and washed with saturated aqueous sodium bicarbonate (100 mL). The aqueous layer was back-extracted with dichloromethane (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 2.80 g of 2-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione as a yellow solid.

Part C

Following the general procedure described in Part G of Examples 127-135, 2-{3-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione (2.80 g, 6.49 mmol) was converted into 1.16 g of 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine.

Part D

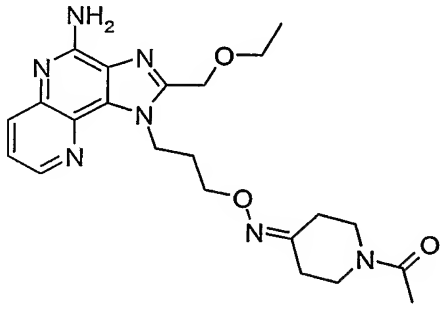
Following the general procedure described in Part E of Example 136, 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.315 g, 1.0 mmol) was converted into 0.234 g of acetone *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime, which was obtained as beige needles, mp 96-97 °C.

MS (APCI) *m/z* 357 $(M + H)^+$;

Anal. calcd for $C_{18}H_{24}N_6O_2$: C, 60.66; H, 6.79; N, 23.58. Found: C, 60.65; H, 6.86; N, 23.96.

Example 139

1-Acetylpiperidin-4-one *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime



To a solution of 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (prepared as described in Parts A-C of Example 138, 0.395 g, 1.25 mmol) in methanol (8 mL) was added 4-acetyl piperidone (0.160 mL, 1.31 mmol). The solution was stirred at room temperature overnight. The solvent

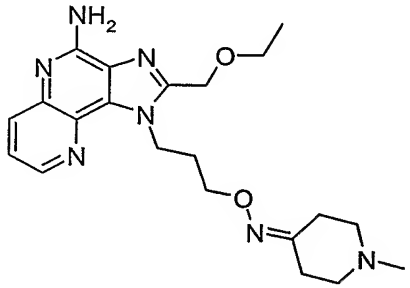
was removed under reduced pressure and the residue was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution using 0-25% CMA in chloroform). The purified material was triturated twice with acetonitrile and dried at elevated temperature under vacuum to provide 0.312 g of 1-acetylpiperidin-4-one *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime as beige needles, mp 162-163 °C.

MS (APCI) *m/z* 440 $(M + H)^+$;

Anal. calcd for $C_{22}H_{29}N_7O_3$: C, 60.12; H, 6.65; N, 22.31. Found: C, 59.89; H, 6.88; N, 22.33.

Example 140

1-Methylpiperidin-4-one *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime



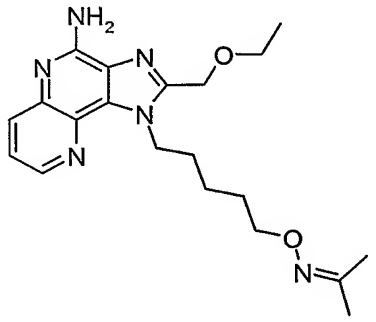
To a solution of 1-[3-(aminooxy)propyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (prepared as described in Parts A-C of Example 138, 0.378 g, 1.19 mmol) in methanol (8 mL) was added *N*-methyl-4-piperidone (0.160 mL, 1.31 mmol). The solution was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution using 0-30% CMA in chloroform). The purified material was crystallized from acetonitrile and dried at elevated temperature under vacuum to provide 93 mg of 1-methylpiperidin-4-one *O*-{3-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime as white needles, mp 111-112 °C.

MS (APCI) *m/z* 412 $(M + H)^+$;

Anal. calcd for $C_{21}H_{29}N_7O_2$: C, 61.29; H, 7.10; N, 23.83. Found: C, 61.05; H, 6.95; N, 23.80.

Example 141

Acetone *O*-{5-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]pentyl}oxime



Part A

Following the general procedures described in Parts A-D of Examples 127-135, 4-chloro-3-nitro[1,5]naphthyridine (10.0 g, 47.7 mmol) was converted into 5-({3-[(2-ethoxyacetyl)amino][1,5]naphthyridin-4-yl}amino)pentyl acetate hydrochloride (approximately 23.3 mmol) using 5-amino-1-pentanol in lieu of 3-amino-1-butanol in Part A and ethoxyacetyl chloride in lieu of butyryl chloride in Part D of Examples 127-135.

Part B

To a solution of the material from Part A in 3:1 ethanol/water was added 6 M K_2CO_3 (11.7 mL, 69.9 mmol). The reaction was stirred at room temperature for 7 days. The reaction was concentrated under reduced pressure and partitioned between dichloromethane (150 mL) and water (75 mL). The aqueous layer was extracted with dichloromethane (50 mL), and the combined organic layers were washed with brine (75 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a brown oil. The oil was dissolved in

methanol (100 mL) and solid potassium carbonate (3 g) was added. The mixture was stirred at room temperature for 1 hour, filtered, and concentrated to an oily residue that was partitioned between dichloromethane (100 mL) and water (50 mL). The aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield an oil. The oil was dissolved in a minimal amount of ethyl acetate. Hexanes were added until the solution become cloudy and mixture was sonicated. A solid formed that was isolated by filtration. The filtrate was concentrated to yield a residue that was triturated with acetonitrile to produce a solid that was isolated by filtration. This last procedure was repeated twice to provide three crops of solid. The solids were combined to afford 4.52 g of 5-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]pentan-1-ol as a pale tan solid.

Part C

Following the general procedure described in Part B of Example 138, 5-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]pentan-1-ol (4.52 g, 14.4 mmol) was converted into 4.65 g of 2-({5-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]pentyl}oxy)-1*H*-isoindole-1,3(2*H*)-dione.

Part D

Following the general procedure described in Part G of Examples 127-135, 2-({5-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]pentyl}oxy)-1*H*-isoindole-1,3(2*H*)-dione (4.65 g, 10.1 mmol) was converted into 1-[5-(aminooxy)pentyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine. In the workup after the reaction mixture was filtered, the filtrate was diluted with brine (30 mL) and chloroform (60 mL). The aqueous layer was extracted with chloroform (2 x 40 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to afford a red solid that was triturated twice with acetonitrile and isolated by filtration to afford 1.35 g of a yellow solid. The filtrates

were combined, concentrated under reduced pressure, and purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-25% CMA in chloroform) to afford additional yellow solid. The solids were combined and dissolved in dichloromethane (150 mL). The solution was washed with saturated aqueous sodium bicarbonate (2 x 75 mL). The combined aqueous layers were back-extracted with dichloromethane (30 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 2.17 g of 1-[5-(aminooxy)pentyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a pale yellow solid.

Part E

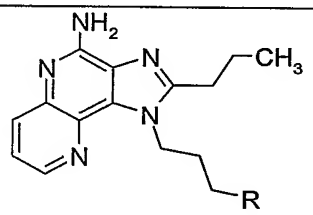
Using the general procedure described in Part E of Example 136, 1-[5-(aminooxy)pentyl]-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (0.60 g, 1.74 mmol) was converted into acetone *O*-{5-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]pentyl}oxime. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution using 0-25% CMA in chloroform) to yield an oil that formed a solid upon standing at room temperature. The solid was dried at elevated temperature under vacuum to yield 0.244 g of acetone *O*-{5-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]pentyl}oxime as beige needles, mp 91-92 °C.
MS (APCI) *m/z* 385 $(M + H)^+$;
Anal. calcd for $C_{20}H_{28}N_6O_2$: C, 62.48; H, 7.34; N, 21.86. Found: C, 62.41; H, 7.64; N, 21.88.

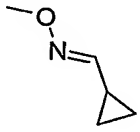
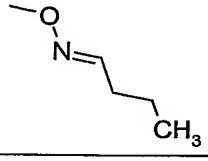
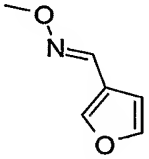
Examples 142-168

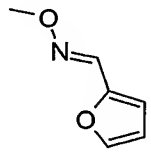
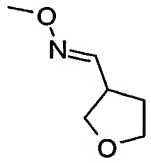
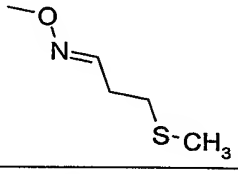
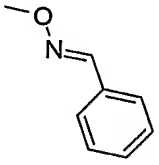
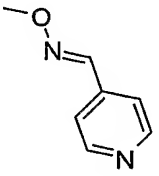
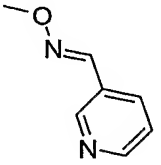
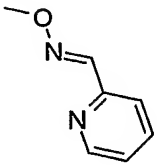
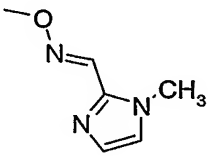
An aldehyde or ketone (0.11 mmol, 1.1 equivalents) from the table below was added to a test tube containing a 1-[3-(aminooxy)propyl]-2-propyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (prepared as described in Parts A-G of Examples 127-135, 29 mg, 0.10 mmol) in methanol (1 mL). The test tubes were capped and shaken overnight at ambient temperature. The solvent was removed by

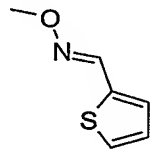
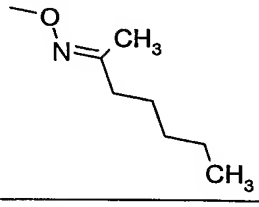
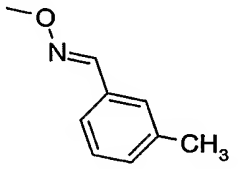
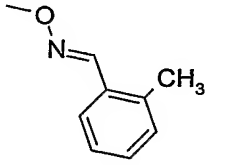
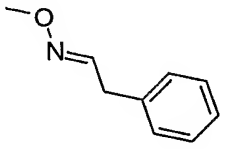
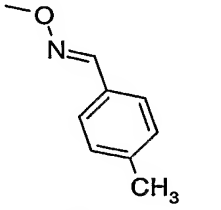
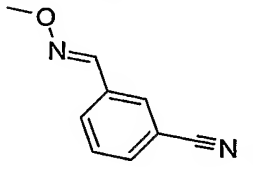
vacuum centrifugation. The compounds were purified by prep HPLC using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

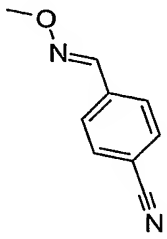
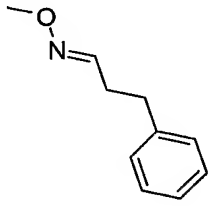
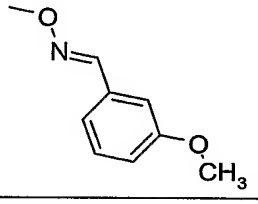
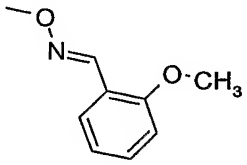
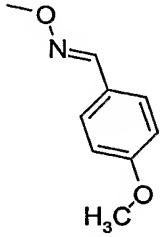
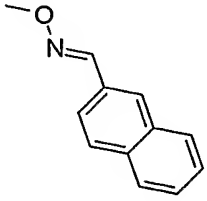
Examples 142-168

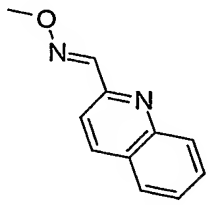
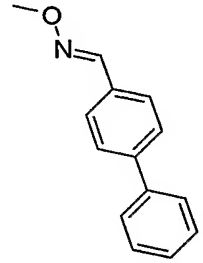
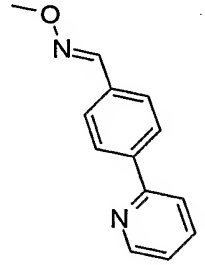


Example	Reagent	R	Measured Mass (M+H)
142	Cyclopropanecarboxaldehyde		353.2096
143	Butyraldehyde		355.2273
144	3-Furaldehyde		379.1894

145	Furfural		379.1919
146	Tetrahydrofuran-3-Carboxaldehyde		383.2163
147	3-(Methylthio)propionaldehyde		387.1989
148	Benzaldehyde		389.2115
149	4-Pyridinecarboxaldehyde		390.2054
150	3-Pyridinecarboxaldehyde		390.2058
151	2-Pyridinecarboxaldehyde		390.2045
152	1-Methyl-2-imidazolecarboxaldehyde		393.2142

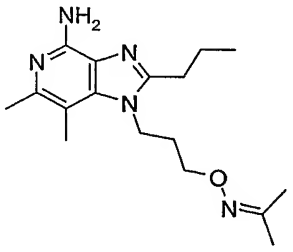
153	2-Thiophenecarboxaldehyde		395.1666
154	2-Heptanone		397.2704
155	*m*-Tolualdehyde		403.2257
156	*o*-Tolualdehyde		403.2234
157	Phenylacetaldehyde		403.2243
158	*p*-Tolualdehyde		403.2263
159	3-Cyanobenzaldehyde		414.2069

160	4-Cyanobenzaldehyde		414.2051
161	3-Phenylpropionaldehyde		417.2429
162	3-Methoxybenzaldehyde		419.2188
163	*o*-Anisaldehyde		419.2211
164	*p*-Anisaldehyde		419.2189
165	2-Naphthaldehyde		439.2252

166	2-Quinolinecarboxaldehyde		440.2214
167	4-Biphenylcarboxaldehyde		465.2410
168	4-(2-Pyridyl)benzaldehyde		466.2325

Example 169

Acetone *O*-[3-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]oxime



Part A

3-Amino-1-propanol (6.92 mL, 90.5 mmol) was added dropwise to a stirred solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (20.0 g, 90.5 mmol) and triethylamine (18.9 mL, 136 mmol) in DMF (300 mL) at room temperature. After 16 hours, the solvent was removed under reduced pressure and the resulting oil was

partitioned between ethyl acetate (450 mL) and water (50 mL). The layers were separated and the organic layer was washed with water (3 x 50 mL). The combined aqueous layers were back-extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting orange solid was triturated with hexanes/ethyl acetate (2:1) and was isolated by filtration to yield 12.43 g of 3-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]propan-1-ol as a yellow solid.

Part B

A mixture of 3-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]propan-1-ol (12.4 g, 47.8 mmol), sodium azide (6.20 g, 95.5 mmol), and cerium (III) chloride heptahydrate (8.90 g, 23.9 mmol) in 9:1 acetonitrile/water (160 mL) was heated at reflux for 16 hours, then was allowed to cool to room temperature. DMF was added and the mixture was filtered. The filter cake was washed with DMF. The filtrate was concentrated under reduced pressure to give an orange solid that was triturated with ethyl acetate to yield 9.60 g of 3-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]propan-1-ol as a yellow solid.

Part C

A mixture of 3-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]propan-1-ol (4.00 g, 15.0 mmol) and 10% palladium on carbon (0.40 g) in acetonitrile (75 mL) was hydrogenated at 50 psi (3.5×10^5 Pa) on a Parr apparatus for 16 hours. The mixture was filtered through CELITE filter agent, which was rinsed with methanol. The filtrate was concentrated under reduced pressure to yield 3.48 g of 3-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]propan-1-ol.

Part D

A mixture of 3-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]propan-1-ol (3.45 g, 14.6 mmol), pyridine hydrochloride (0.64 g, 5.5 mmol) and trimethyl orthobutyrate (2.60 mL, 16.1 mmol) in toluene (100 mL) was

heated to reflux. Additional trimethyl orthobutyrate was added (1.1 equivalents). The mixture was heated at reflux for 16 hours. The mixture was allowed to cool to room temperature and 3.21 g of the product, 3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propan-1-ol, was isolated by filtration.

Part E

Diisopropyl azodicarboxylate (372 µL, 1.89 mmol) was added to a stirred solution of 3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propan-1-ol (500 mg, 1.72 mmol), triphenylphosphine (496 mg, 1.89 mmol), and *N*-hydroxyphthalimide (308 mg, 1.89 mmol) in DMF (17 mL) at room temperature. After 4 hours, the solvent was removed under reduced pressure to afford an oil that was triturated with ethyl acetate to generate a pink solid. The solid was isolated by filtration and washed with ethyl acetate to yield 630 mg of 2-[3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione as a pink powder.

Part F

Anhydrous hydrazine (108 µL, 3.45 mmol) was added to a stirred suspension of 2-[3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (500 mg, 1.15 mmol) in ethanol (8 mL) at room temperature. After 30 minutes, dichloromethane (2.5 mL) was added to help dissolve the starting material. The solution was stirred for 4 hours, then was concentrated under reduced pressure to yield crude 7-[3-(aminooxy)propyl]-5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridine. Acetone (6 mL) and methanol (6 mL) were added to the crude 7-[3-(aminooxy)propyl]-5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridine and the resulting solution was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure. The residue was treated with 1 M NaOH and the mixture was sonicated for 1 minute to provide a white solid that was isolated by filtration and washed with water. The solid was dried under

vacuum with heating at 70 °C to provide 300 mg of the product, acetone *O*-[3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propyl]oxime, as a white solid.

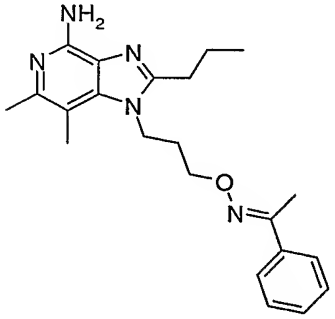
Part G

A solution of acetone *O*-[3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propyl]oxime (290 mg, 0.84 mmol) and triphenylphosphine (443 mg, 1.69 mmol) in 1,2-dichlorobenzene (8.5 mL) was heated at 120 °C for 3 days. The solution was allowed to cool to room temperature and methanol (1 mL) and trifluoroacetic acid (2 mL) were added. After the stirred solution was heated at 60 °C for 2 hours, the solution was allowed to cool to room temperature for 16 hours, and then was heated again at 60 °C for 6 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane (50 mL) and saturated aqueous sodium carbonate (10 mL). The aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were washed with saturated aqueous sodium carbonate (3 x 10 mL), dried over sodium sulfate, filtered, and concentrated. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 15-40% CMA in chloroform) to yield a solid that was recrystallized from acetonitrile to provide 191 mg of the product, acetone *O*-[3-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]oxime as a white powder, mp 105.0-106.0 °C.

Anal. Calcd for $C_{17}H_{27}N_5O$: C, 64.32; H, 8.57; N, 22.06. Found: C, 64.07; H, 8.43; N, 21.87.

Example 170

(1*E*)-1-Phenylethanone *O*-[3-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]oxime



Part A

A solution of 2-[3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (prepared as described in Parts A-E of Example 169, 8.50 g, 19.6 mmol) and triphenylphosphine (10.3 g, 39.2 mmol) in 1,2-dichlorobenzene (200 mL) was heated at 125 °C for 2 days, then was allowed to stand at room temperature for 3 days. The solvent was removed under reduced pressure. To the resulting residue was added methanol (40 mL) and 1 M HCl (20 mL). The solution was heated at 50 °C for 5 h, was allowed to cool to room temperature, and was concentrated under reduced pressure. Water (20 mL) was added and the mixture was extracted with chloroform (3 x 10 mL). The aqueous layer was adjusted to pH 11 with the addition of 1 M NaOH. The aqueous layer was extracted with chloroform (4 x 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with CMA in chloroform) to yield 1.00 g of 1-[3-(aminooxy)propyl]-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine.

Part B

A solution of 1-[3-(aminooxy)propyl]-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (0.64 g, 2.3 mmol) and acetophenone (325 µL, 2.76

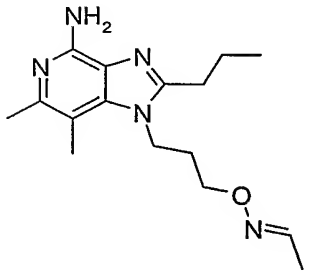
mmol) in methanol (23 mL) was stirred overnight at room temperature, then heated at 50 °C for 4 hours. Pyridine hydrochloride (100 mg) was added to the solution and stirring was continued at 50 °C overnight. Additional pyridine hydrochloride was added and the solution was heated at reflux for 5 hours. The solvent was removed under reduced pressure and the resulting off-white solid was partitioned between chloroform (100 mL) and saturated aqueous sodium carbonate (30 mL). The aqueous layer was extracted with chloroform (3 x 30 mL). The combined organic layers were washed with saturated aqueous sodium carbonate (2 x 20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 5-30% CMA in chloroform) to yield a solid that was triturated with acetonitrile and dried under vacuum at 70 °C overnight to provide 105 mg of (1*E*)-1-phenylethanone *O*-[3-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]oxime as a white powder, mp 125.0-127.0 °C.

Anal. Calcd for $C_{22}H_{29}N_5O$: C, 69.63; H, 7.70; N, 18.45. Found: C, 69.41; H, 7.73; N, 18.36.

The product was obtained as a 90:10 mixture of *E*:*Z* isomers.

Example 171

Ethanal *O*-[3-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]oxime



Part A

2-[3-(5,6-Dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (prepared as described in Parts A-E of Example 169, 5.94 g, 13.7 mmol) was converted into 3.88 g of ethanal *O*-[3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propyl]oxime using acetaldehyde in lieu of acetone in the procedure described in Part F of Example 169. The product was obtained as a 55:45 mixture of *E*:*Z* isomers.

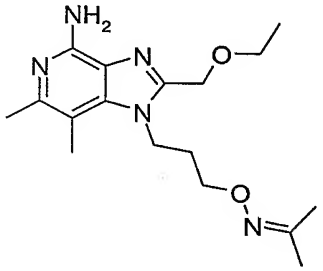
Part B

Using the method described in Part G of Example 169, ethanal *O*-[3-(5,6-dimethyl-8-propyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)propyl]oxime (3.86 g, 11.7 mmol) was converted into 1.2 g of ethanal *O*-[3-(4-amino-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)propyl]oxime, which was isolated as a white powder, mp 117.0-119.0 °C. Anal. Calcd for $C_{16}H_{25}N_5O$: C, 63.34; H, 8.31; N, 23.08. Found: C, 63.27; H, 8.55; N, 23.08.

The product was obtained as a 55:45 mixture of *E*:*Z* isomers.

Example 172

Acetone *O*-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}oxime



Part A

To a stirred suspension of 3-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]propan-1-ol (prepared as described in Parts A-B of Example 169, 1.00 g, 3.76 mmol) in dichloromethane (38 mL) at 0 °C were added triethylamine (0.68 mL, 4.9 mmol) and acetic anhydride (0.39 mL, 4.1 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The suspension was filtered and the filter cake was washed with dichloromethane. The filtrate was transferred to a separatory funnel and was extracted with saturated aqueous sodium bicarbonate (20 mL). The aqueous layer was back extracted with dichoromethane (3 x 20 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (3 x 20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give 0.48 g of 3-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]propyl acetate as yellow oil that crystallized upon standing at room temperature for 1 hour.

Part B

A mixture of 3-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]propyl acetate (0.43 g, 1.4 mmol) and 10% platinum on carbon (43 mg) in acetonitrile (14 mL) was hydrogenated at 50 psi (3.5×10^5 Pa) on a Parr apparatus for 3 hours. The mixture was filtered through CELITE filter agent, which was rinsed with chloroform. The filtrate was concentrated under reduced pressure to

yield 0.36 g of 3-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]propyl acetate as a white solid.

Part C

Ethoxyacetyl chloride (175 mg, 1.43 mmol) and triethylamine (236 μL, 1.69 mmol) were sequentially added to a solution of 3-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]propyl acetate (0.36 g, 1.3 mmol) in dichloromethane (13 mL) at 0 °C. The solution was allowed to warm to room temperature and was stirred for 2.5 hours. Additional ethoxyacetyl chloride (20 mg) was added. After another hour, the solvent was removed under reduced pressure and the crude 3-({8-[(ethoxyacetyl)amino]-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl}amino)propyl acetate was carried on to the next step.

Part D

A solution of 6 M potassium carbonate (0.9 mL, 5.2 mmol) was added to a solution of crude 3-({8-[(ethoxyacetyl)amino]-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl}amino)propyl acetate from Part C in 3:1 ethanol/water (12 mL) at room temperature. The solution was stirred for 3 days, then was heated to 80 °C. More 6 M potassium carbonate (3 mL) was added after 1 day. After another day, 6 M potassium carbonate (5 mL) was added again. The temperature was increased to 85 °C and stirring was continued one more day. The solvent was removed under reduced pressure and the residue was partitioned between chloroform (100 mL) and saturated aqueous sodium bicarbonate (30 mL). The layers were separated and the aqueous layer was extracted with chloroform (3 x 20 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate (2 x 20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield 0.35 g of 3-[8-(ethoxymethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]propan-1-ol as a white solid.

Part E

Following the general method described in Part E of Example 169, 3-[8-(ethoxymethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]propan-1-ol (0.90 g, 3.0 mmol) was converted into 2-{3-[8-(ethoxymethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione. The product was isolated by filtering the reaction directly, washing the filter cake with ethyl acetate, and drying the solid under vacuum to provide 0.90 g of 2-{3-[8-(ethoxymethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione as a pink powder.

Part F

Anhydrous hydrazine (190 μL, 6.0 mmol) was added to a stirred suspension of 2-{3-[8-(ethoxymethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione (0.90 g, 2.0 mmol) in ethanol (15 mL) at room temperature. After approximately 16 hours, acetone (6 mL) was added and the reaction was stirred for 1 day. The solvent was removed under reduced pressure. The residue was treated with 1 M NaOH and the mixture was sonicated for 1 minute to provide a white solid that was isolated by filtration and washed with water. The solid was dried under vacuum with heating to provide 0.54 g of the product, acetone *O*-{3-[8-(ethoxymethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]propyl}oxime.

Part G

Following the general method described in Part G of Example 169, acetone *O*-{3-[8-(ethoxymethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]propyl}oxime (0.54 g, 1.5 mmol) was converted into 0.18 g of acetone *O*-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}oxime. The solvent system used during the chromatographic purification was 5-30% CMA in chloroform (gradient elution) to afford the product as a white solid, which was triturated with acetonitrile and isolated by filtration to provide

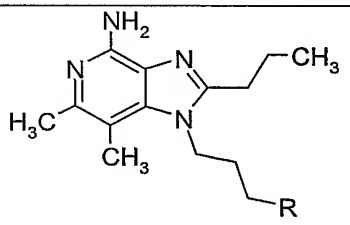
acetone *O*-{3-[4-amino-2-(ethoxymethyl)-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl]propyl}oxime as a white powder, mp 123.0-125.0 °C.

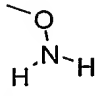
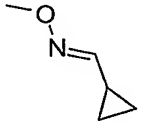
Anal. Calcd for $C_{17}H_{27}N_5O_2$: C, 61.24; H, 8.16; N, 21.00. Found: C, 61.15; H, 8.31; N, 21.27.

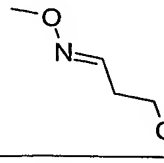
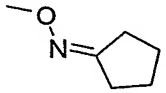
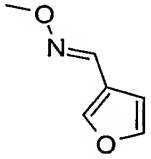
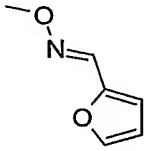
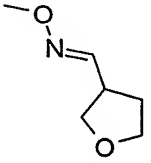
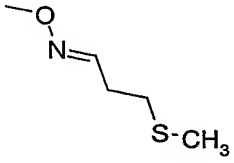
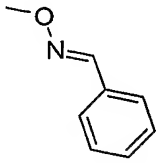
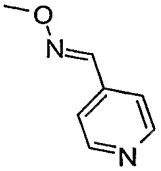
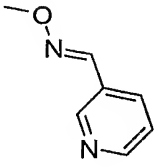
Examples 173-199

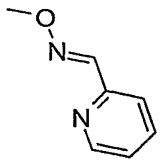
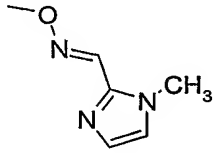
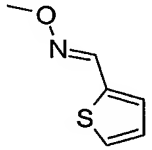
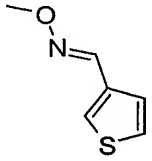
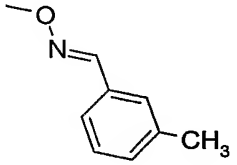
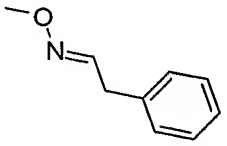
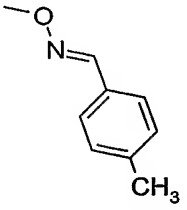
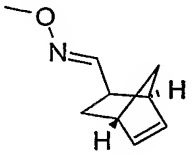
An aldehyde or ketone (0.12 mmol, 1.2 equivalents) from the table below was added to a test tube containing 1-[3-(aminooxy)propyl]-6,7-dimethyl-2-propyl-1*H*-imidazo[4,5-*c*]pyridin-4-amine (27 mg, 0.10 mmol) in methanol (1 mL). The test tubes were capped and shaken overnight at ambient temperature. The solvent was removed by vacuum centrifugation. The compounds were purified as described for Examples 142-168. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

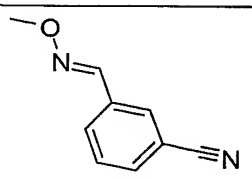
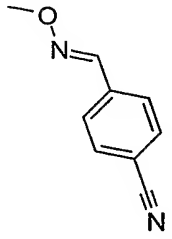
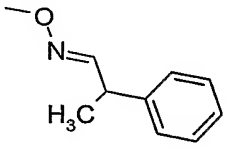
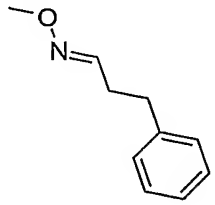
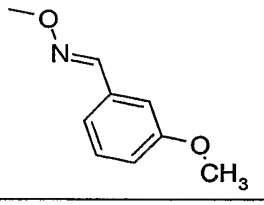
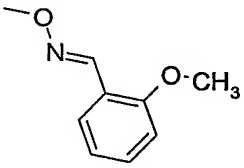
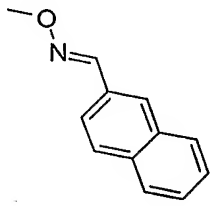
Examples 173-199

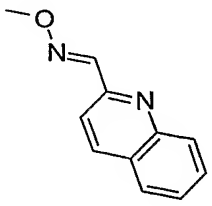
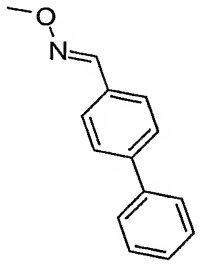


Example	Reagent	R	Measured Mass (M+H)
	Starting Material Only – No Reagent Added		278.1955
173	Cyclopropanecarboxaldehyde		330.2270

174	Butryaldehyde		332.2452
175	Cyclopentanone		344.2455
176	3-Furaldehyde		356.2081
177	Furfural		356.2097
178	Tetrahydrofuran-3-carboxyaldehyde		360.2401
179	3-(Methylthio)propionaldehyde		364.2198
180	Benzaldehyde		366.2307
181	4-Pyridinecarboxaldehyde		367.2243
182	3-Pyridinecarboxaldehyde		367.2252

183	2-Pyridinecarboxaldehyde		367.2249
184	1-Methyl-2-imidazolecarboxaldehyde		370.2368
185	2-Thiophenecarboxaldehyde		372.1884
186	3- Thiophenecarboxaldehyde		372.1871
187	*m*-Tolualdehyde		380.2460
188	Phenylacetaldehyde		380.2444
189	*p*-Tolualdehyde		380.2445
190	5-Norbornene-2-carboxyaldehyde		382.2620

191	3-Cyanobenzaldehyde		391.2263
192	4-Cyanobenzaldehyde		391.2276
193	2-Phenylpropionaldehyde		394.2601
194	3-Phenylpropionaldehyde		394.2617
195	3-Methoxybenzaldehyde		396.2401
196	*o*-Anisaldehyde		396.2407
197	2-Naphthaldehyde		416.2451

198	2-Quinolinecarboxaldehyde		417.2426
199	4-Biphenylcarboxaldehyde		442.2584

Examples 200-202

Part A

A solution of 2-(2-aminoethoxy)ethanol (30.3 g, 288 mmol) in a minimal amount of dichloromethane was added dropwise to a stirred mixture of 4-chloro-3-nitroquinoline (50.0 g, 240 mmol), potassium carbonate (33.1 g, 240 mmol), and triethylamine (36.4 g mL, 360 mmol) in DMF (200 mL) at 0 °C. A yellow precipitate formed and more dichloromethane (several mL) was added. The mixture was allowed to warm to room temperature and stir overnight. A yellow solid was isolated by filtration, washed with water and dichloromethane, and dried. The filtrate was washed twice with brine, dried over magnesium sulfate, and filtered. Additional orange solid was isolated from the filtrate. The solids dried in a vacuum oven to afford 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethanol.

Part B

A mixture of 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethanol (66.2 g, 239 mmol) and 5% platinum on carbon (7.5 g) in ethanol (250 mL) was hydrogenated at approximately 30 psi (2.1×10^5 Pa) on a Parr apparatus overnight. Magnesium sulfate was added to the mixture, which was then filtered through CELITE filter

agent. The filtrate was concentrated to provide 43.0 g of crude 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethanol as a yellow solid.

Part C

A mixture of 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethanol (43.0 g, 155 mmol) and pyridine hydrochloride (1.79 g, 15.5 mmol) in toluene (200 mL) and dichloroethane (100 mL) was heated at reflux until a solution formed. The solution was allowed to cool to room temperature, then was cooled to 0 °C. Triethyl orthopropionate (30.1 g, 171 mmol) was added and the mixture was heated at reflux for 3 hours. The solution was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was diluted with chloroform and 4 M NaOH was added to adjust the pH to 9. The mixture was filtered and the isolated solid dissolved when it was washed with water and chloroform. The filtrate was transferred to a separatory funnel and washed twice with brine. The combined aqueous layers were back-extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered, and concentrated to provide 40.0 g of 2-[2-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethanol as a tan solid.

Part D

The general procedure described in Part A of Example 1 was used to convert 2-[2-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethanol (35.6 g, 125 mmol) into 2-{2-[2-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione. For the work-up, the solvent was removed and the residue was dissolved in chloroform (300 mL). To the solution was added 6 M HCl. Some of the solvent was removed from the mixture under reduced pressure, but the product did not precipitate so the mixture was transferred to a separatory funnel. The organic layer was removed. To the aqueous layer was added 6 M NaOH (240 mL), causing a precipitate to form. The mixture was extracted with chloroform three times. The later organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified

by flash chromatography (silica gel, gradient elution with 0-5% methanol in dichloromethane) to provide 11.0 g of 2-{2-[2-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione.

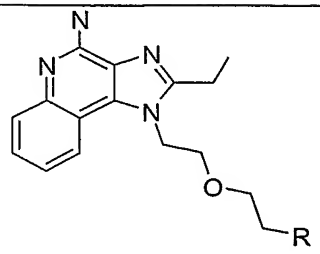
Part E

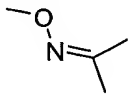
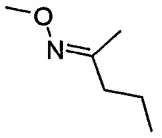
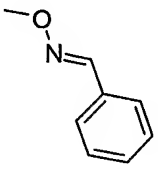
To a solution of 2-{2-[2-(2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione (11.0 g, 25.5 mmol) in chloroform (150 mL) was added mCPBA (11.4 g, 51.1 mmol). The solution was stirred at room temperature for 2 hours. Concentrated ammonium hydroxide (100 mL) was added, followed by *p*-toluenesulfonyl chloride (5.40 g, 28.1 mmol). The mixture was stirred overnight at room temperature. The mixture was transferred to a separatory funnel and was washed twice with 5% aqueous ammonium chloride and once with aqueous sodium carbonate solution, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography (silica gel, gradient elution with 0-5% methanol in dichloromethane) to provide 6 g of 1-{2-[2-(aminooxy)ethoxy]ethyl}-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine.

Part F

The method described in Part D of Example 1 can be used to treat 1-{2-[2-(aminooxy)ethoxy]ethyl}-2-ethyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine with an aldehyde or ketone shown in the table below to provide a compound with a structure shown in the table below.

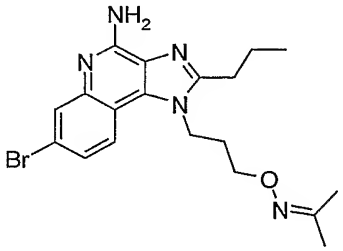
Examples 200-202



Example	Ketone or Aldehyde	R
200	acetone	
201	2-pentanone	
202	benzaldehyde	

Example 203

Acetone *O*-[3-(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime



Part A

A mixture of triethyl orthoformate (154 g, 1.04 mol) and Meldrum's acid (142 g, 0.983 mol) was heated to 55 °C for 4 hours. After cooling to 50 °C, a

solution of 3-bromoaniline (162.6 g, 0.945 mol) in ethanol (300 mL) was added such that the temperature of the reaction was maintained between 50-55 °C. After half of the 3-bromoaniline had been added, stirring became difficult due to the formation of solids, so more ethanol (1 L) was added to facilitate stirring. Upon complete addition, the reaction was cooled to room temperature, and the solids were collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless, and the product was dried at 65 °C under vacuum to afford 287 g of 5-[(3-bromophenylimino)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.19 (brd, J = 12.8 Hz, 1H), 8.60 (d, J = 14.0 Hz, 1H), 7.44-7.38 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.18 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H), 1.75 (s, 6H).

Part B

7-Bromoquinolin-4-ol was prepared in accordance with the literature procedure (D. Dibyendu et al., *J. Med. Chem.*, *41*, 4918-4926 (1998)) or by thermolysis of 5-[(3-bromophenylimino)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione in DOWTHERM A heat transfer fluid and had the following spectral properties:

^{1}H NMR (300 MHz, d_6-DMSO) δ 11.70 (brs, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.44 (dd, J = 8.7, 1.9 Hz, 1H), 6.05 (d, J = 7.5 Hz, 1H).

Part C

A stirred suspension of 7-bromoquinolin-4-ol (162 g, 0.723 mol) in propionic acid (1500 mL) was brought to 110 °C. Nitric acid (85 g of 70%) was added dropwise over 1 h such that the temperature was maintained between 110-115 °C. After half of the nitric acid had been added, stirring became difficult due to the formation of solids and an additional 200 mL of propionic acid was added. Upon complete addition, the reaction was stirred for 1 hour at 110°C, cooled to room temperature, and the solid was collected by filtration. The filter cake was washed

with ice cold ethanol until the washings were nearly colorless (800 mL), and the product was dried at 60 °C under vacuum to afford 152 g of 7-bromo-3-nitro-quinolin-4-ol as a pale yellow solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 13.0 (brs, 1H), 9.22 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 8.7, 1.9 Hz, 1H).

Part D

7-Bromo-3-nitroquinolin-4-ol (42 g, 156 mmol) was suspended in $POCl_3$ (130 mL) and brought to 102 °C under an atmosphere of N_2. After 45 min, all of the solids had dissolved, so the reaction was cooled to room temperature. The resulting solids were collected by filtration, washed with H_2O, and then partitioned with CH_2Cl_2 (3 L) and 2M Na_2CO_3 (500 mL). The organic layer was separated, washed with H_2O (1x), dried over Na_2SO_4, filtered, and concentrated to afford 33.7 g of 7-bromo-4-chloro-3-nitroquinoline as a beige solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.90 (dd, J = 8.9, 2.1 Hz, 1H).

Part E

To a solution of 7-bromo-4-chloro-3-nitroquinoline (10.00 g, 34.78 mmol) in dichloromethane (140 mL) was added triethylamine (10.2 mL, 73.1 mmol). The solution was cooled to 0 °C, and 3-amino-1-butanol (2.80 mL, 36.5 mmol) was added. The solution was stirred overnight at ambient temperature and then filtered to collect a precipitate. The precipitate was washed with dichloromethane and water. The filtrate was washed with saturated aqueous sodium bicarbonate and then added to the precipitate. The mixture was concentrated under reduced pressure. Methanol and toluene were added several times and removed under reduced pressure. The resulting solid was dried under high vacuum to provide 11.34 g of 3-[(7-bromo-3-nitroquinolin-4-yl)amino]propan-1-ol as a yellow solid.

Part F

A solution of sodium dithionate (27.5 g, 158 mmol) in water (60 mL) was added to a solution of 3-[(7-bromo-3-nitroquinolin-4-yl)amino]propan-1-ol (10.3 g, 31.6 mmol) in ethanol (175 mL), and the mixture was stirred vigorously for four hours at ambient temperature. The solvent was removed under reduced pressure, and the residue was partitioned between dichloromethane/chloroform/methanol (500 mL) and saturated aqueous sodium bicarbonate (200 mL). The aqueous layer was separated and extracted with chloroform (5 x 200 mL), and the combined organic fractions were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide 7.27 g of 3-[(3-amino-7-bromoquinolin-4-yl)amino]propan-1-ol.

Part G

A mixture of 3-[(3-amino-7-bromoquinolin-4-yl)amino]propan-1-ol (7.2 g, 24 mmol), pyridine hydrochloride (1.05 g, 9.09 mmol) and trimethyl orthobutyrate (4.05 mL, 25.5 mmol) in toluene (240 mL) was heated at reflux for two hours under an atmosphere of nitrogen. The solvent was removed under reduced pressure, and the residue was dissolved in methanol (100 mL). Aqueous sodium hydroxide (15 mL of 6 M) was added to the solution, and the resulting mixture was stirred for two hours at ambient temperature. A portion of the solvent was removed under reduced pressure, and the resulting mixture was adjusted to pH 7 with the addition of 6 N hydrochloric acid. The mixture was then extracted with chloroform (4 x 150 mL), and the combined extracts were washed sequentially with saturated aqueous sodium bicarbonate (40 mL) and brine (30 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. An analysis by nuclear magnetic resonance spectroscopy indicated the presence of starting material, and the procedure was repeated using 1 mL trimethyl orthobutyrate and heating at reflux for one hour. Following the work-up procedure, the resulting solid was triturated with ethyl acetate and isolated by filtration to provide 7.30 g of 3-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propan-1-ol.

Part H

A modification of the method described in Part A of Example 1 was followed using 3-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propan-1-ol (4.60 g, 13.2 mmol), triphenylphosphine (4.17 g, 15.9 mmol), diisopropyl azodicarboxylate (3.13 mL, 15.9 mmol), and *N*-hydroxyphthalimide (2.59 g, 15.9 mmol). After the solvent was removed under reduced pressure, the residue was dissolved in chloroform (200 mL), washed sequentially with saturated aqueous sodium bicarbonate (2 x 30 mL) and brine (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was triturated twice with ethyl acetate to provide 4.68 g of 2-[3-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione.

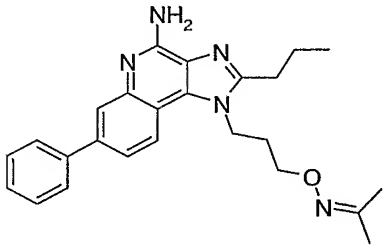
Part I

To a solution of 2-[3-(7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propoxy]-1*H*-isoindole-1,3(2*H*)-dione (1.00 g, 2.03 mmol) in chloroform (20 mL) at room temperature and under an atmosphere of nitrogen was added mCPBA (1.00 g, 4.06 mmol). The reaction was stirred for 1.5 hours and cooled to 0 °C. Concentrated ammonium hydroxide (4 mL) was added followed by *p*-toluenesulfonyl chloride (425 mg, 2.23 mmol) in portions. The mixture was stirred for one hour at 0 °C, and then acetone (20 mL) was added. The reaction was stirred vigorously for one hour and then concentrated under reduced pressure. The residue was partitioned between chloroform (200 mL) and saturated aqueous sodium bicarbonate (40 mL). The organic layer was separated and washed sequentially with saturated aqueous sodium bicarbonate (50 mL) and brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified twice by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-35% CMA in chloroform), then was recrystallized twice from acetonitrile, triturated with ethyl acetate, and recrystallized from acetonitrile to afford 41 mg of acetone *O*-[3-(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a white powder, mp 182.0-183.0 °C.

Anal. Calcd for $C_{19}H_{24}BrN_5O$: C, 54.55; H, 5.78; N, 16.74. Found: C, 54.65; H, 5.75; N, 16.64.

Example 204

Acetone *O*-[3-(4-amino-7-phenyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime

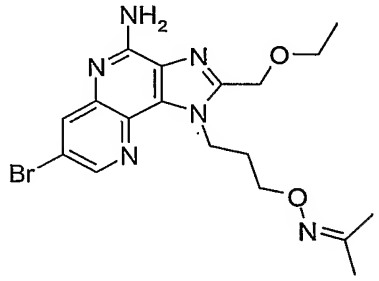


In a pressure vessel under a nitrogen atmosphere, acetone *O*-[3-(4-amino-7-bromo-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime (500 mg, 1.20 mmol), phenylboronic acid (219 mg, 1.80 mmol), a solution of palladium (II) acetate (2.7 mg, 0.012 mmol) in hot toluene (0.5 mL), triphenylphosphine (9.5 mg, 0.036 mmol), and 2 M aqueous sodium carbonate (0.72 mL, 1.44 mmol) were combined in 5:1 *n*-propanol:water (2.4 mL). The solution was placed under vacuum and back-filled with nitrogen three times. The pressure vessel was sealed and heated at 100 °C overnight, then was allowed to cool to ambient temperature. Chloroform (60 mL) was added and the mixture was washed with water (2 x 10 mL) and brine (10 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-35% CMA in chloroform) to yield a solid that was triturated twice with acetonitrile and isolated to yield 278 mg of acetone *O*-[3-(4-amino-7-phenyl-2-propyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]oxime as a white powder, mp 164.0-165.0 °C.

Anal. Calcd for $C_{25}H_{29}N_5O \cdot 0.75H_2O$: C, 69.99; H, 7.17; N, 16.32. Found: C, 70.20; H, 7.36; N, 16.39.

Example 205

Acetone *O*-{3-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime



Part A

A mixture of triethyl orthoformate (10 mL, 60.1 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (40.9 g, 0.23 mol) (Meldrum's acid) was heated at 92 °C for 90 minutes and then cooled to 70 °C over one hour. 3-Amino-5-bromopyridine (40.9 g, 0.20 mol) was slowly added over 10 minutes with an ethanol rinse while maintaining the reaction temperature between 60 and 70 °C. The reaction was then heated for an additional 20 minutes and allowed to cool to room temperature. The reaction mixture was filtered and washed with ethanol (150 mL) yielding a tan solid. The solid was dried under vacuum for 2 hours to yield 59.14 g of 5-{[(5-bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione as a light yellow crystalline solid, mp 200-202 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.26 (d, J = 14.3 Hz, 1H), 8.80 (d, J = 2.3 Hz, 1H), 8.62 (d, J = 14.3 Hz, 1H), 8.56(d, J = 1.9 Hz, 1H), 8.44-8.40 (m, 1H), 1.68 (s, 6H).

Part B

5-{[(5-Bromopyridin-3-yl)imino]methyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (59 g, 0.18 mol) was slowly added to DOWTHERM A heat transfer fluid (2000 mL) over a period of 5 minutes at 235-238 °C. Following addition, the reaction was maintained for an additional 5 minutes and then allowed to cool to 40 °C. A brown precipitate formed, which was filtered and washed with hexanes (150

mL). The brown solid was suspended in an ethanol/water mixture (90:10, 1500 mL), heated to a boil for 30 minutes, isolated by filtration, and washed with ethanol (200 mL) to yield 30.8 g of 7-bromo[1,5]naphthyridin-4-ol as a dark brown powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.81(br s, 1H), 8.69(d, J = 1.9 Hz, 1H), 8.21 (d, J = 1.9 Hz, 1H), 7.95(d, J = 7.7 Hz, 1H), 6.22 (d, J = 7.5 Hz, 1H).

Part C

A mixture of 7-bromo[1,5]naphthyridin-4-ol (33 g, 0.147 mol) and fuming nitric acid (350 mL) was heated at reflux (90 °C internal reaction vessel temperature) for 3 hours. The reaction mixture was cooled to 50 °C, poured over 1 L of ice and adjusted to pH 2-3 with the addition of 50% aqueous NaOH. The resulting precipitate was filtered, washed with water, and dried over vacuum for 3 days to yield 25.1 g of 7-bromo-3-nitro[1,5]naphthyridin-4-ol as a yellow crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 13.06(br s, 1H), 9.26(s, 1H), 8.88 (d, J = 2.0 Hz, 1H), 8.37(d, J = 2.0 Hz, 1H).

Part D

Phosphorous oxychloride (16.76 g, 10.19 mL, 109.3 mmol) was added slowly dropwise to a suspension of 7-bromo-3-nitro[1,5]naphthyridin-4-ol (21.09 g, 78.1 mmol) in DMF (250 mL) at ambient temperature and stirred for 3 hours. The reaction mixture was then added to ice water (400 mL) with stirring. A solid precipitate formed, which was isolated by vacuum filtration and washed with water. The material was dried under high vacuum at ambient temperature to yield 7-bromo-4-chloro-3-nitro[1,5]naphthyridine as a tan solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51(s, 1H), 9.36 (d, J = 2.2 Hz, 1H), 9.02(d, J = 2.1 Hz, 1H).

Part E

To a solution of 7-bromo-4-chloro-3-nitro[1,5]naphthyridine (22.53 g, 78.10 g) in dichloromethane (260 mL) at room temperature was added triethylamine (14.2 mL, 102 mmol). The solution was cooled to 0 °C and 3-amino-1-propanol (6.57 mL, 85.9 mmol) was added. The solution was stirred for 20 minutes at room temperature and then was concentrated under reduced pressure to yield a yellow solid. Water (250 mL) was added to the solid, and the mixture was sonicated for 10 minutes. The solid was isolated by filtration, washed with water, and dried at 70 °C under vacuum to afford 22.60 g of 3-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]propan-1-ol as a yellow powder.

Part F

3-[(7-Bromo-3-nitro[1,5]naphthyridin-4-yl)amino]propan-1-ol (22.60 g, 69.08 mmol) was converted into 25.30 g of 3-[(7-bromo-3-nitro[1,5]naphthyridin-4-yl)amino]propyl acetate, which contained a trace amount of 4-dimethylaminopyridine, using the method described in Part B of Examples 127-135.

Part G

3-[(7-Bromo-3-nitro[1,5]naphthyridin-4-yl)amino]propyl acetate (25.3 g, 68.5 mmol) was converted into 3-[(3-amino-7-bromo[1,5]naphthyridin-4-yl)amino]propyl acetate using the method described in Part C of Examples 127-135.

Part H

The general procedures described in Parts D and E of Examples 127-135 were used to convert the material from Part G (approximately 68.5 mmol) into 22.2 g of 3-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propan-1-ol using ethoxyacetyl chloride in lieu of butyryl chloride in Part D of Examples 127-135. Extra dichloromethane (250 mL) was used in the acylation reaction, and the reaction time was lengthened to overnight. In the cyclization reaction, the reaction was heated for 45 minutes instead of 7 hours.

Part I

Diisopropyl azodicarboxylate (6.47 mL, 32.9 mmol) was added dropwise over ten minutes to a stirred solution of 3-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propan-1-ol (10.0 g, 27.4 mmol), triphenylphosphine (8.62 g, 32.9 mmol), and *N*-hydroxyphthalimide (5.36 g, 32.9 mmol) in DMF (110 mL) at 0 °C. The reaction was allowed to warm to room temperature and was stirred overnight. The solvent was removed under reduced pressure to afford a solid that was slurried in ethyl acetate, isolated by filtration, washed with ethyl acetate, and dried under vacuum to yield 11.45 g of 2-{3-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione as a pink solid.

Part J

mCPBA (11.06 g, 44.88 mmol) was added to a stirred solution of 2-{3-[7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propoxy}-1*H*-isoindole-1,3(2*H*)-dione (11.40 g, 22.44 mmol) in chloroform (225 mL) at room temperature. After 1 hour, additional mCPBA (1.5 g) was added and stirring was continued for another 30 minutes. The solution was cooled to 0 °C and concentrated ammonium hydroxide (45 mL) was added followed by *p*-toluenesulfonyl chloride (added in portions, 4.71 g, 24.7 mmol). After 1 hour, additional *p*-toluenesulfonyl chloride (1.0 g) was added and stirring was continued at 0 °C. After another 2 hours, more *p*-toluenesulfonyl chloride (0.4 g) was added, then the reaction was stirred at room temperature for 1 hour. Acetone (225 mL) was added and the reaction was stirred overnight at room temperature. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in chloroform (700 mL) and the solution was washed with saturated aqueous sodium bicarbonate (2 x 100 mL) and brine (70 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material, which contained about 50% of the unreacted *N*-oxide intermediate, was dissolved in

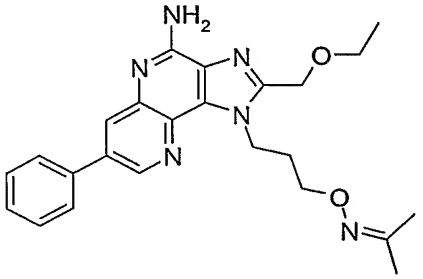
chloroform (220 mL). The solution was cooled to 0 °C and concentrated ammonium hydroxide (20 mL) was added, followed by portionwise addition of *p*-toluenesulfonyl chloride (4 g). The reaction was allowed to warm to room temperature and was stirred overnight. The mixture was filtered again and the filtrate was treated to the workup described above. The crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-25% CMA in chloroform), recrystallized from ethyl acetate/hexanes, and dried under vacuum to provide 2.8 g of acetone *O*-{3-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime as a beige powder, mp 128.0-130.0 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (d, J = 2.2 Hz, 1H), 8.11 (d, J = 2.2 Hz, 1H), 7.13 (s, 2H), 4.84 (t, J = 7.1 Hz, 2H), 4.77 (s, 2H), 4.03 (t, J = 6.0 Hz, 2H), 3.56 (q, J = 7.0 Hz, 2H), 2.28-2.15 (m, 2H), 1.75 (s, 3H), 1.73 (s, 3H), 1.16 (t, J = 7.0 Hz, 3H);

HRMS (EI) calcd for $C_{18}H_{23}BrN_6O_2$ $(M+H)^+$: 435.1144. Found: 435.1142.

Example 206

Acetone *O*-{3-[4-amino-2-(ethoxymethyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime



In a pressure vessel under a nitrogen atmosphere, acetone *O*-{3-[4-amino-7-bromo-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime (2.50 g, 5.74 mmol), phenylboronic acid (1.05 g, 8.61 mmol), palladium (II) acetate (13 mg, 0.057 mmol), triphenylphosphine (45 mg, 0.17 mmol), and 2 M aqueous sodium carbonate (3.45 mL, 6.89 mmol) were combined in 5:1 *n*-propanol:water (12

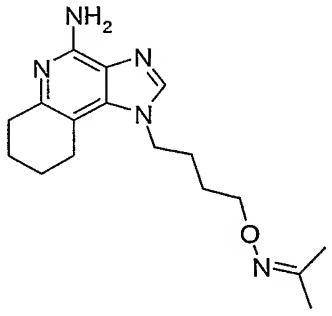
mL). The solution was placed under vacuum and back-filled with nitrogen three times. The pressure vessel was sealed and heated at 100 °C for 2 days, then was allowed to cool to ambient temperature. Chloroform (200 mL) was added and the mixture was washed with water (40 mL) and brine (40 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-25% CMA in chloroform) to yield 2.4 g of acetone *O*-{3-[4-amino-2-(ethoxymethyl)-7-phenyl-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-1-yl]propyl}oxime as a yellow powder, mp 134.0-136.0 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (d, J = 2.2 Hz, 1H), 8.13 (d, J = 2.2 Hz, 1H), 7.92-7.80 (m, 2H), 7.57-7.39 (m, 3H), 6.94 (s, 2H), 4.91 (dd, J = 7.6, 6.6 Hz, 2H), 4.79 (s, 2H), 4.06 (t, J = 6.0 Hz, 2H), 3.57 (q, J = 7.0 Hz, 2H), 2.35-2.21 (m, 2H), 1.77 (s, 3H), 1.76 (s, 3H), 1.18 (t, J = 7.0 Hz, 3H);

HRMS (EI) calcd for $C_{24}H_{28}N_6O_2$ $(M+H)^+$: 433.2352. Found: 433.2342.

Example 207

Acetone *O*-[4-(4-amino-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]oxime



Part A

Platinum (IV) oxide (3.5 g) was added to a solution of 4-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (prepared as described in Example 9 of U.S. Patent No. 6,664,264, 4.00 g, 15.6 mmol) in trifluoroacetic acid (200 mL), and the mixture was shaken under hydrogen pressure for 2 days on a Parr apparatus. The

reaction mixture was concentrated under reduced pressure, carefully diluted with methanol, and filtered through a layer of CELITE filter agent. The filtrate was concentrated under reduced pressure. The resulting residue was diluted with a solution of 4 M hydrogen chloride in 1,4-dioxane (100 mL) and stirred at ambient temperature for 1 hour; then 4 M aqueous sodium hydroxide was added to adjust the mixture to pH 13. The mixture was transferred to a separatory funnel, and dichloromethane was added. The mixture was shaken and allowed to stand overnight at ambient temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 1.0 g of 4-(4-amino-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol as a white solid.

Part B

A cloudy solution of 4-(4-amino-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (1.0 g, 3.8 mmol), triphenylphosphine (1.49 g, 5.7 mmol) and *N*-hydroxyphthalimide (0.93 g, 5.7 mmol) in tetrahydrofuran (50 mL) was cooled to approximately 0 °C; then diisopropyl azodicarboxylate (1.33 mL, 6.8 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and was stirred for 5 hours. The solvent was removed under reduced pressure, and the resulting solid was purified by chromatography on silica gel (gradient elution with 0-10% methanol in dichloromethane with a small amount of concentrated ammonium hydroxide added) to provide 600 mg of 2-[4-(4-amino-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione as a yellow solid.

Part C

Anhydrous hydrazine (94 mg, 2.96 mmol) was added to 2-[4-(4-amino-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione (600 mg, 1.48 mmol) in ethanol (25 mL) at ambient temperature. The

reaction was stirred overnight, and additional hydrazine (2 equivalents) was added. After stirring for 2 hours at ambient temperature, the reaction was concentrated under reduced pressure. The residue was diluted with dichloromethane and concentrated under reduced pressure three times to remove the hydrazine and then dried under vacuum to provide 550 mg of impure 1-[4-(aminooxy)butyl]-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an orange solid.

Part D

Acetone (59 μL, 0.80 mmol) was added to a solution of the material from Part C (200 mg, 0.73 mmol) in methanol (25 mL). The solution was stirred for 30 minutes, and then more acetone (1 equivalent) was added. After 1 hour, the cloudy white solution was concentrated under reduced pressure. The crude product was purified by chromatography (silica gel, gradient elution with 0-10% methanol in dichloromethane with a small amount of concentrated ammonium hydroxide added). The appropriate fractions were combined and concentrated to yield 100 mg of acetone *O*-[4-(4-amino-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butyl]oxime as an off-white solid, mp 151.0-153.0 °C.

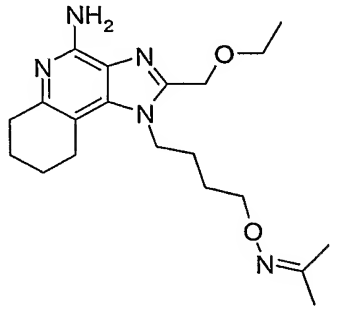
^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (s, 1H), 5.90 (br s, 2H), 4.28 (t, J = 7.1 Hz, 2H), 3.94 (t, J = 6.3 Hz, 2H), 2.93 (m, 2H), 2.67 (m, 2H), 1.81-1.72 (m, 12H), 1.56 (m, 2H); ^{13}C NMHR (300 MHz, DMSO-d_6) δ 154.1, 150.0, 146.6, 142.8, 137.3, 126.6, 105.6, 71.9, 45.9, 32.4, 28.8, 26.1, 23.6, 23.0, 21.6, 15.5;

MS (ESI) *m/z* 316 $(M + H)^+$;

HRMS (EI) calcd for $C_{17}H_{25}N_5O$ $(M+H)^+$: 316.2137. Found: 316.2142.

Example 208

Acetone *O*-{4-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}oxime



Part A

The methods described in Parts B and C of Example 1 can be used to treat 4-[2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol with mCPBA and ammonium hydroxide to provide 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol.

Part B

The method described in Part A of Example 207 can be used to reduce 4-[4-amino-2-(ethoxymethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol to 4-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol.

Part C

The method described in Part A of Example 1 can be used to convert 4-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol to 2-{4-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione.

Part D

The method described in Part F of Example 169 can be used to treat 2-{4-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-

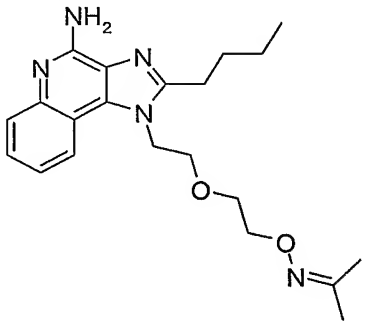
yl)butoxy]-1*H*-isoindole-1,3(2*H*)-dione with anhydrous hydrazine to provide 1-[4-(aminooxy)butyl]-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine.

Part E

The method described in Example 3 can be used to treat 1-[4-(aminooxy)butyl]-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine with acetone to provide acetone *O*-{4-[4-amino-2-(ethoxymethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]butyl}oxime.

Example 209

Acetone *O*-{2-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethyl}oxime



Part A

Phosphorous oxychloride (84.3 g, 0.55 mol) was added to a stirred suspension of 3-nitroquinolin-4-ol (95.0 g, 0.50 mol) in DMF (500 mL), and an exotherm was observed. After the addition was complete, the solution was heated on a steam bath for 15 minutes. The solution was poured over ice to precipitate 4-chloro-3-nitroquinoline. The 4-chloro-3-nitroquinoline was isolated by filtration, washed with water, and pressed dry. The 4-chloro-3-nitroquinoline was dissolved in dichloromethane (1 L) and the solution was dried over magnesium sulfate and filtered. 2-(2-Aminoethoxy)ethanol (60.7 g, 0.6 mol) and triethylamine (104 mL, 0.75 mol) were added to the filtrate. The resulting solution was heated at reflux for

30 minutes. The mixture was concentrated under reduced pressure. The residue was dissolved in dilute aqueous hydrochloric acid and filtered. Ammonium hydroxide was added to the filtrate and a yellow solid formed. The solid was isolated by filtration, washed with water, and dried to provide 104.5 g of 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethanol as a yellow solid.

Part B

A mixture of 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethanol (55.5 g, 0.2 mol), acetic anhydride (37.6 mL, 0.4 mol), and pyridine (250 mL) was heated at reflux for 30 minutes. The solution was allowed to cool to ambient temperature and was concentrated under reduced pressure to remove about 50-75% of the pyridine. The residual solution was poured into water to precipitate the product as an oil which solidified upon stirring. The solid was isolated by filtration, washed with water, and dried. The crude product was recrystallized from 2-propanol (200 mL) to provide 55.6 g of 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethyl acetate as a bright yellow solid.

Part C

A mixture of 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethyl acetate (104.7 g), magnesium sulfate (30 g) and 5% platinum on carbon (5 g) in ethyl acetate was hydrogenated at 30 psi (2.1×10^5 Pa) overnight on a Parr apparatus. The mixture was filtered through CELITE filter agent. The filtrate was concentrated under reduced pressure to provide an oil that was used in the next step.

Part D

Valeryl chloride (39 mL, 0.33 mol) was added to a solution of the material from Part C in acetonitrile (1 L) at room temperature. After 3 hours, a solid precipitated from the solution. The mixture was allowed to stand overnight and the solid was isolated by filtration, washed with acetonitrile, and used in the next step.

Part E

The crude material from Part D was divided into four high pressure reaction vessels and 5% ammonia in methanol was added. The reaction vessels were heated at 150 °C for 6 hours. The vessels were allowed to cool to room temperature, and then their contents were combined and concentrated under reduced pressure. Dichloromethane and water were added to the resulting oil, and a precipitate formed that was isolated by filtration. The tan solid was dried to provide 85 g of 2-[2-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethanol.

Part F

A cloudy solution of 2-[2-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethanol (10.0 g, 31.9 mmol), triphenylphosphine (14.2 g, 70.2 mmol) and *N*-hydroxyphthalimide (8.85 g, 70.2 mmol) in tetrahydrofuran (250 mL) was cooled to approximately 0 °C; then diisopropyl azodicarboxylate (10.7 mL, 70.2 mmol) was added dropwise. The reaction was allowed to warm to ambient temperature and was stirred overnight. Additional tetrahydrofuran (100 mL) followed by DMF (25 mL) was added to the mixture, and the mixture was stirred overnight at room temperature. Over a 1 day period, more diisopropyl azodicarboxylate, triphenylphosphine, and *N*-hydroxyphthalimide (1 equivalent of each) and DMF (50 mL) were added to the mixture. Chloroform (200 mL) was added and the solution was washed with saturated aqueous sodium bicarbonate (5 x 500 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was subjected to flash chromatography (silica gel, eluted with 1.5% methanol in chloroform) to yield 12.46 g of 2-{2-[2-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione.

Part G

mCPBA (12.6 g, 36.5 mmol) was added to a stirred solution of 2-{2-[2-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethoxy}-1*H*-isoindole-1,3(2*H*)-dione (12.89 g, 28.1 mmol) in dichloromethane (130 mL) at room temperature. After 1.3

hours, additional mCPBA (1.8 g) was added, and stirring was continued for another 30 minutes. Concentrated ammonium hydroxide (65 mL) was added followed by *p*-toluenesulfonyl chloride (12.57 g, 36.5 mmol), which was added slowly. The reaction was stirred at room temperature overnight. The organic phase was isolated, dried over sodium sulfate, and concentrated under reduced pressure. A small portion of the crude product was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 0-40% CMA in chloroform) to yield 1-{2-[2-(aminooxy)ethoxy]ethyl}-2-butyl-1*H*-imidazo[4,5-*c*]quinoline in approximately 80% purity. This material was used without further purification in the next step.

Part H

Acetone (2 mL) was added to a solution of the material from Part G (0.78 g, 2.3 mmol) in methanol (13 mL). The solution was stirred overnight at room temperature. The solution was concentrated under reduced pressure to yield an oil that was purified by flash chromatography (silica gel, elution with 0.5% methanol in chloroform). Analysis by ^{1}H NMR indicated that the *N*-oxide was still present. The material was treated with ammonium hydroxide and *p*-toluenesulfonyl chloride as described in Part G. The organic phase was isolated, diluted with chloroform, washed with 1% aqueous sodium carbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was triturated with hexanes at room temperature overnight and then was isolated by filtration and dried under vacuum at 70 °C to provide 0.06 g of acetone *O*-{2-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethyl}oxime as a yellow solid, mp 116.5-117.5 °C.

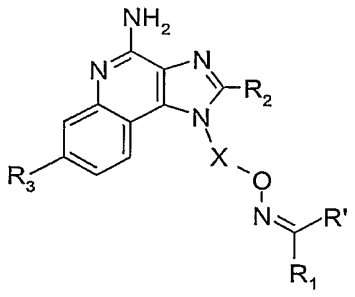
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 8.3 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 7.21 (t, J = 8.2 Hz, 1H), 6.43 (s, 2H), 4.70 (t, J = 5.2 Hz, 2H), 3.92 (m, J = 5.9 Hz, 4H), 3.51 (t, J = 4.7, 2H), 2.94 (t, J = 7.9, 2H), 1.84 (pentet, J = 7.4, 2H), 1.71 (s, 3H), 1.64 (s, 3H), 1.45 (sextet, J = 7.4 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H);

MS (APCI) *m/z* 384 $(M + H)^+$;

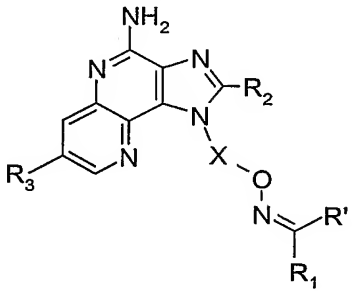
Anal. calcd for $C_{21}H_{29}N_5O_2$: C, 65.77; H, 7.62; N, 18.26. Found: C, 65.49; H, 7.89; N, 18.37.

Exemplary Compounds

Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIa and VIIIa) and the following R', R_1, X, R_2 and R_3 substituents, wherein each line of the table is matched with Formula IIIa or VIIIa to represent a specific embodiment of the invention.



IIIa



VIIIa

R_1	R'	X	R_2	R_3
hydrogen	hydrogen	$-(CH_2)_3-$	hydrogen	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_3-$	hydrogen	phenyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethyl	phenyl
hydrogen	hydrogen	$-(CH_2)_3-$	propyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_3-$	propyl	phenyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethoxymethyl	phenyl
hydrogen	hydrogen	$-(CH_2)_3-$	butyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_3-$	butyl	phenyl
hydrogen	hydrogen	$-(CH_2)_4-$	hydrogen	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_4-$	hydrogen	phenyl
hydrogen	hydrogen	$-(CH_2)_4-$	ethyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_4-$	ethyl	phenyl
hydrogen	hydrogen	$-(CH_2)_4-$	propyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_4-$	propyl	phenyl
hydrogen	hydrogen	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl

hydrogen	hydrogen	$-(CH_2)_4-$	ethoxymethyl	phenyl
hydrogen	hydrogen	$-(CH_2)_4-$	butyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_4-$	butyl	phenyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
hydrogen	methyl	$-(CH_2)_3-$	hydrogen	3-pyridyl
hydrogen	methyl	$-(CH_2)_3-$	hydrogen	phenyl
hydrogen	methyl	$-(CH_2)_3-$	ethyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_3-$	ethyl	phenyl
hydrogen	methyl	$-(CH_2)_3-$	propyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_3-$	propyl	phenyl
hydrogen	methyl	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_3-$	ethoxymethyl	phenyl
hydrogen	methyl	$-(CH_2)_3-$	butyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_3-$	butyl	phenyl
hydrogen	methyl	$-(CH_2)_4-$	hydrogen	3-pyridyl
hydrogen	methyl	$-(CH_2)_4-$	hydrogen	phenyl
hydrogen	methyl	$-(CH_2)_4-$	ethyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_4-$	ethyl	phenyl
hydrogen	methyl	$-(CH_2)_4-$	propyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_4-$	propyl	phenyl
hydrogen	methyl	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_4-$	ethoxymethyl	phenyl
hydrogen	methyl	$-(CH_2)_4-$	butyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_4-$	butyl	phenyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl

hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	hydrogen	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	hydrogen	phenyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	ethyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	ethyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	propyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	propyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	ethoxymethyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	butyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	butyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	hydrogen	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	hydrogen	phenyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	ethyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	ethyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	propyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	propyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	ethoxymethyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	butyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	butyl	phenyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl

hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
methyl	methyl	$-(CH_2)_3-$	hydrogen	3-pyridyl
methyl	methyl	$-(CH_2)_3-$	hydrogen	phenyl
methyl	methyl	$-(CH_2)_3-$	ethyl	3-pyridyl
methyl	methyl	$-(CH_2)_3-$	ethyl	phenyl
methyl	methyl	$-(CH_2)_3-$	propyl	3-pyridyl
methyl	methyl	$-(CH_2)_3-$	propyl	phenyl
methyl	methyl	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
methyl	methyl	$-(CH_2)_3-$	ethoxymethyl	phenyl
methyl	methyl	$-(CH_2)_3-$	butyl	3-pyridyl
methyl	methyl	$-(CH_2)_3-$	butyl	phenyl
methyl	methyl	$-(CH_2)_4-$	hydrogen	3-pyridyl
methyl	methyl	$-(CH_2)_4-$	hydrogen	phenyl
methyl	methyl	$-(CH_2)_4-$	ethyl	3-pyridyl
methyl	methyl	$-(CH_2)_4-$	ethyl	phenyl
methyl	methyl	$-(CH_2)_4-$	propyl	3-pyridyl
methyl	methyl	$-(CH_2)_4-$	propyl	phenyl
methyl	methyl	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
methyl	methyl	$-(CH_2)_4-$	ethoxymethyl	phenyl
methyl	methyl	$-(CH_2)_4-$	butyl	3-pyridyl
methyl	methyl	$-(CH_2)_4-$	butyl	phenyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl

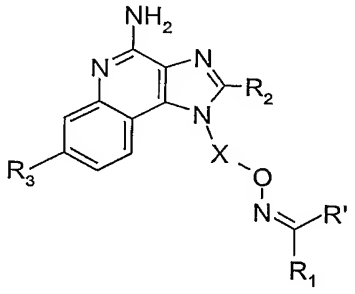
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
methyl	3-pyridyl	$-(CH_2)_3-$	hydrogen	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_3-$	hydrogen	phenyl
methyl	3-pyridyl	$-(CH_2)_3-$	ethyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_3-$	ethyl	phenyl
methyl	3-pyridyl	$-(CH_2)_3-$	propyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_3-$	propyl	phenyl
methyl	3-pyridyl	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_3-$	ethoxymethyl	phenyl
methyl	3-pyridyl	$-(CH_2)_3-$	butyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_3-$	butyl	phenyl
methyl	3-pyridyl	$-(CH_2)_4-$	hydrogen	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_4-$	hydrogen	phenyl
methyl	3-pyridyl	$-(CH_2)_4-$	ethyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_4-$	ethyl	phenyl
methyl	3-pyridyl	$-(CH_2)_4-$	propyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_4-$	propyl	phenyl
methyl	3-pyridyl	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_4-$	ethoxymethyl	phenyl
methyl	3-pyridyl	$-(CH_2)_4-$	butyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_4-$	butyl	phenyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
methyl	hydrogen	$-(CH_2)_3-$	hydrogen	3-pyridyl
methyl	hydrogen	$-(CH_2)_3-$	hydrogen	phenyl
methyl	hydrogen	$-(CH_2)_3-$	ethyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_3-$	ethyl	phenyl
methyl	hydrogen	$-(CH_2)_3-$	propyl	3-pyridyl

methyl	hydrogen	$-(CH_2)_3-$	propyl	phenyl
methyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl	phenyl
methyl	hydrogen	$-(CH_2)_3-$	butyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_3-$	butyl	phenyl
methyl	hydrogen	$-(CH_2)_4-$	hydrogen	3-pyridyl
methyl	hydrogen	$-(CH_2)_4-$	hydrogen	phenyl
methyl	hydrogen	$-(CH_2)_4-$	ethyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_4-$	ethyl	phenyl
methyl	hydrogen	$-(CH_2)_4-$	propyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_4-$	propyl	phenyl
methyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl	phenyl
methyl	hydrogen	$-(CH_2)_4-$	butyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_4-$	butyl	phenyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	hydrogen	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	hydrogen	phenyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	ethyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	ethyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	propyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	propyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	butyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	butyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	hydrogen	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	hydrogen	phenyl

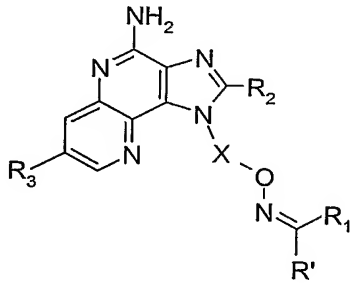
3-pyridyl	hydrogen	$-(CH_2)_4-$	ethyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	ethyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	propyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	propyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	butyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	butyl	phenyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
3-pyridyl	methyl	$-(CH_2)_3-$	hydrogen	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_3-$	hydrogen	phenyl
3-pyridyl	methyl	$-(CH_2)_3-$	ethyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_3-$	ethyl	phenyl
3-pyridyl	methyl	$-(CH_2)_3-$	propyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_3-$	propyl	phenyl
3-pyridyl	methyl	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_3-$	ethoxymethyl	phenyl
3-pyridyl	methyl	$-(CH_2)_3-$	butyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_3-$	butyl	phenyl
3-pyridyl	methyl	$-(CH_2)_4-$	hydrogen	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_4-$	hydrogen	phenyl
3-pyridyl	methyl	$-(CH_2)_4-$	ethyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_4-$	ethyl	phenyl
3-pyridyl	methyl	$-(CH_2)_4-$	propyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_4-$	propyl	phenyl
3-pyridyl	methyl	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_4-$	ethoxymethyl	phenyl
3-pyridyl	methyl	$-(CH_2)_4-$	butyl	3-pyridyl

3-pyridyl	methyl	$-(CH_2)_4-$	butyl	phenyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl

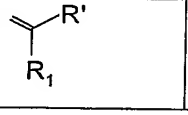
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIa and VIIIa) and the following R', R_1, X, R_2 and R_3 substituents, wherein R' and R_1 join to form a ring, and each line of the table is matched with Formula IIIa or VIIIa to represent a specific embodiment of the invention.

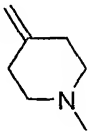
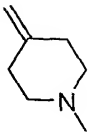
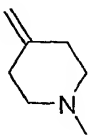
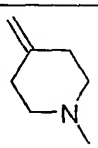
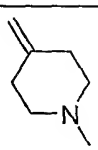
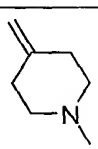
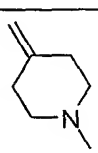
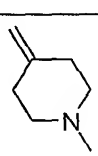


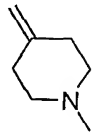
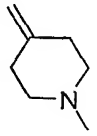
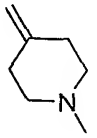
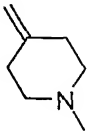
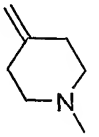
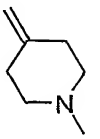
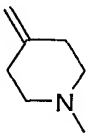
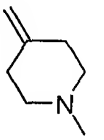
IIIa

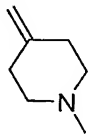
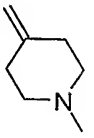
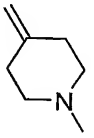
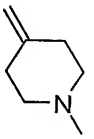
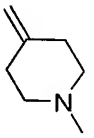
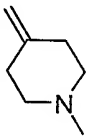
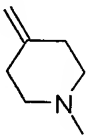
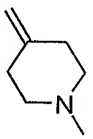


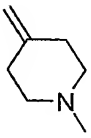
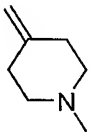
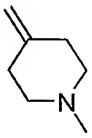
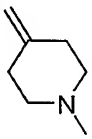
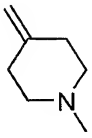
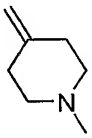
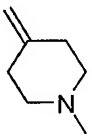
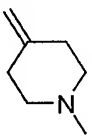
VIIIa

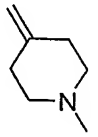
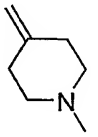
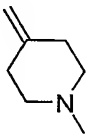
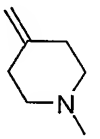
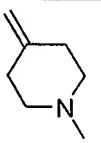
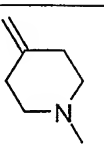
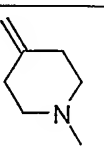
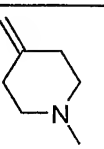
	X	R_2	R_3

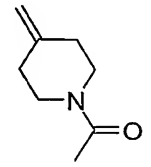
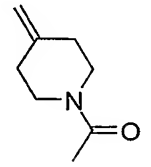
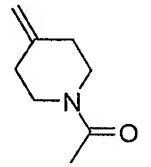
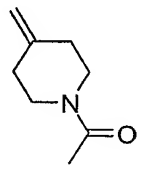
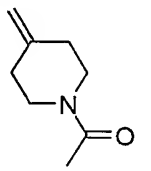
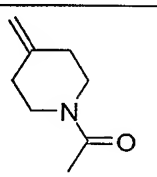
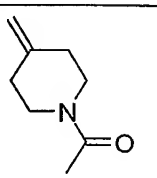
	$-(CH_2)_3-$	hydrogen	3-pyridyl
	$-(CH_2)_3-$	hydrogen	phenyl
	$-(CH_2)_3-$	ethyl	3-pyridyl
	$-(CH_2)_3-$	ethyl	phenyl
	$-(CH_2)_3-$	propyl	3-pyridyl
	$-(CH_2)_3-$	propyl	phenyl
	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_3-$	ethoxymethyl	phenyl

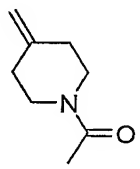
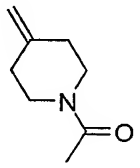
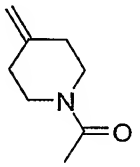
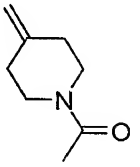
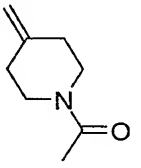
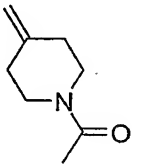
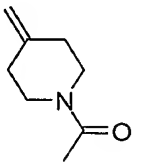
	$-(CH_2)_3-$	butyl	3-pyridyl
	$-(CH_2)_3-$	butyl	phenyl
	$-(CH_2)_4-$	hydrogen	3-pyridyl
	$-(CH_2)_4-$	hydrogen	phenyl
	$-(CH_2)_4-$	ethyl	3-pyridyl
	$-(CH_2)_4-$	ethyl	phenyl
	$-(CH_2)_4-$	propyl	3-pyridyl
	$-(CH_2)_4-$	propyl	phenyl

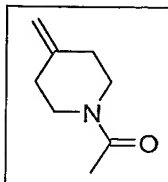
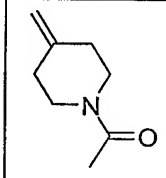
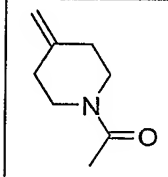
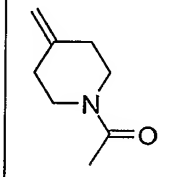
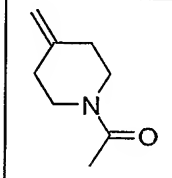
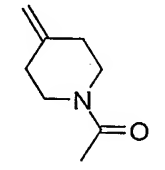
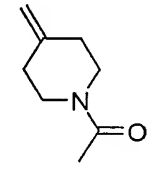
	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_4-$	ethoxymethyl	phenyl
	$-(CH_2)_4-$	butyl	3-pyridyl
	$-(CH_2)_4-$	butyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl

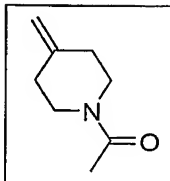
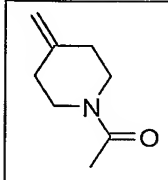
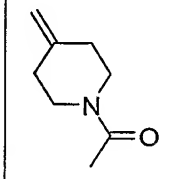
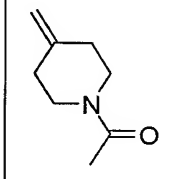
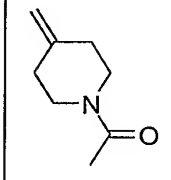
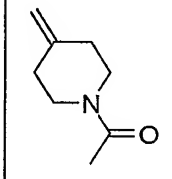
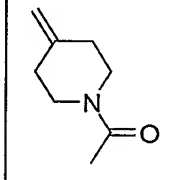
	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl

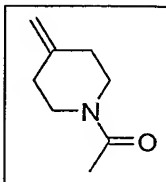
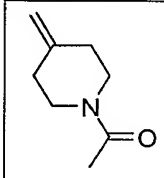
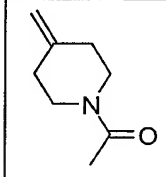
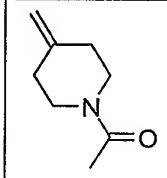
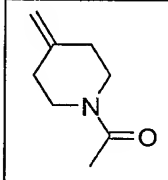
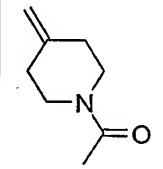
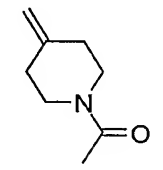
	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl

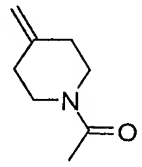
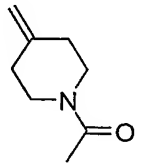
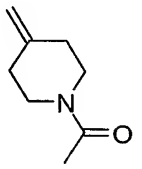
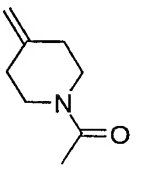
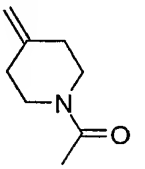
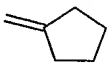
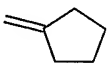
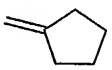
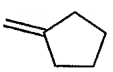
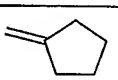
	$-(CH_2)_3-$	hydrogen	3-pyridyl
	$-(CH_2)_3-$	hydrogen	phenyl
	$-(CH_2)_3-$	ethyl	3-pyridyl
	$-(CH_2)_3-$	ethyl	phenyl
	$-(CH_2)_3-$	propyl	3-pyridyl
	$-(CH_2)_3-$	propyl	phenyl
	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl

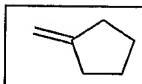
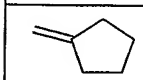
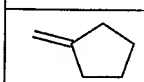
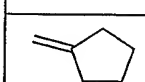
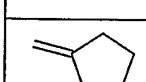
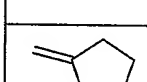
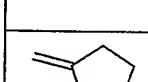
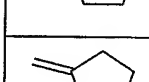
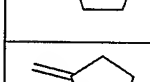
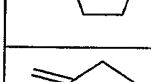
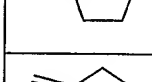
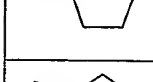
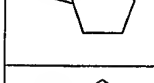
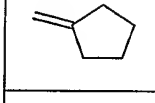
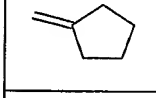
	$-(CH_2)_3-$	ethoxymethyl	phenyl
	$-(CH_2)_3-$	butyl	3-pyridyl
	$-(CH_2)_3-$	butyl	phenyl
	$-(CH_2)_4-$	hydrogen	3-pyridyl
	$-(CH_2)_4-$	hydrogen	phenyl
	$-(CH_2)_4-$	ethyl	3-pyridyl
	$-(CH_2)_4-$	ethyl	phenyl

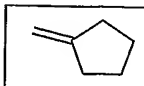
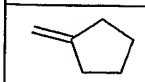
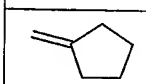
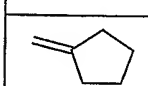
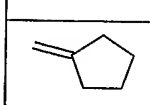
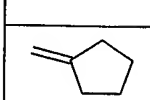
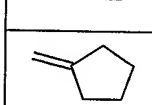
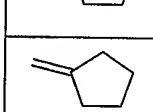
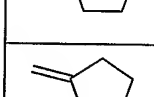
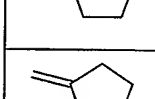
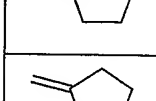
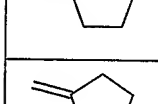
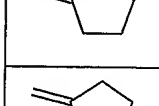
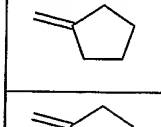
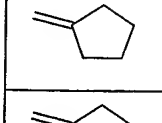
	$-(CH_2)_4-$	propyl	3-pyridyl
	$-(CH_2)_4-$	propyl	phenyl
	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_4-$	ethoxymethyl	phenyl
	$-(CH_2)_4-$	butyl	3-pyridyl
	$-(CH_2)_4-$	butyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl

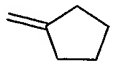
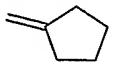
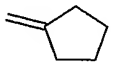
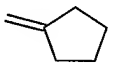
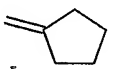
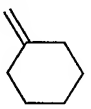
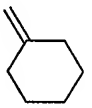
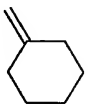
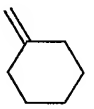
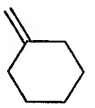
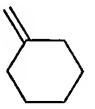
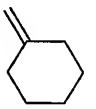
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl

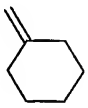
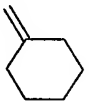
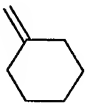
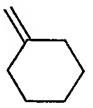
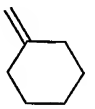
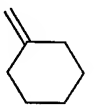
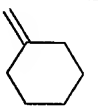
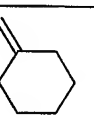
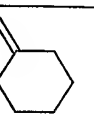
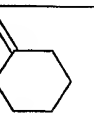
	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl

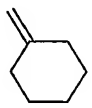
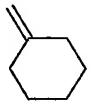
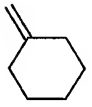
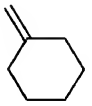
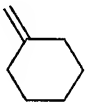
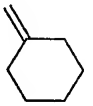
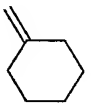
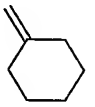
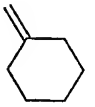
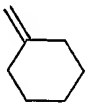
	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
	$-(CH_2)_3-$	hydrogen	3-pyridyl
	$-(CH_2)_3-$	hydrogen	phenyl
	$-(CH_2)_3-$	ethyl	3-pyridyl
	$-(CH_2)_3-$	ethyl	phenyl
	$-(CH_2)_3-$	propyl	3-pyridyl

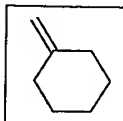
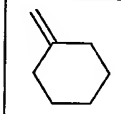
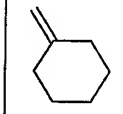
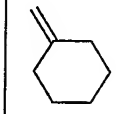
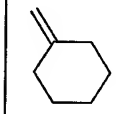
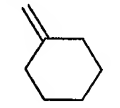
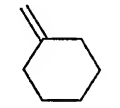
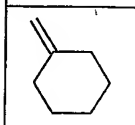
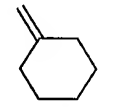
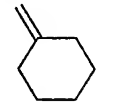
	$-(CH_2)_3-$	propyl	phenyl
	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_3-$	ethoxymethyl	phenyl
	$-(CH_2)_3-$	butyl	3-pyridyl
	$-(CH_2)_3-$	butyl	phenyl
	$-(CH_2)_4-$	hydrogen	3-pyridyl
	$-(CH_2)_4-$	hydrogen	phenyl
	$-(CH_2)_4-$	ethyl	3-pyridyl
	$-(CH_2)_4-$	ethyl	phenyl
	$-(CH_2)_4-$	propyl	3-pyridyl
	$-(CH_2)_4-$	propyl	phenyl
	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_4-$	ethoxymethyl	phenyl
	$-(CH_2)_4-$	butyl	3-pyridyl
	$-(CH_2)_4-$	butyl	phenyl

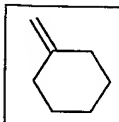
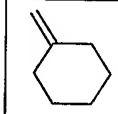
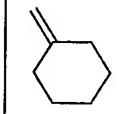
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl

	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl
	$-(CH_2)_3-$	hydrogen	3-pyridyl
	$-(CH_2)_3-$	hydrogen	phenyl
	$-(CH_2)_3-$	ethyl	3-pyridyl
	$-(CH_2)_3-$	ethyl	phenyl
	$-(CH_2)_3-$	propyl	3-pyridyl
	$-(CH_2)_3-$	propyl	phenyl
	$-(CH_2)_3-$	ethoxymethyl	3-pyridyl

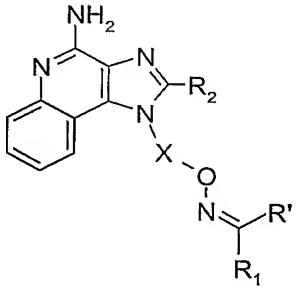
	$-(CH_2)_3-$	ethoxymethyl	phenyl
	$-(CH_2)_3-$	butyl	3-pyridyl
	$-(CH_2)_3-$	butyl	phenyl
	$-(CH_2)_4-$	hydrogen	3-pyridyl
	$-(CH_2)_4-$	hydrogen	phenyl
	$-(CH_2)_4-$	ethyl	3-pyridyl
	$-(CH_2)_4-$	ethyl	phenyl
	$-(CH_2)_4-$	propyl	3-pyridyl
	$-(CH_2)_4-$	propyl	phenyl
	$-(CH_2)_4-$	ethoxymethyl	3-pyridyl

	$-(CH_2)_4-$	ethoxymethyl	phenyl
	$-(CH_2)_4-$	butyl	3-pyridyl
	$-(CH_2)_4-$	butyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	ethyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	propyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	propyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	3-pyridyl

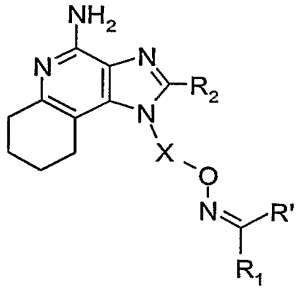
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl	phenyl
	$-CH_2C(CH_3)_2CH_2-$	butyl	3-pyridyl
	$-CH_2C(CH_3)_2CH_2-$	butyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen	phenyl
	$-(CH_2)_2O(CH_2)_2-$	ethyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	ethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	propyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	propyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	3-pyridyl

	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl	phenyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	3-pyridyl
	$-(CH_2)_2O(CH_2)_2-$	butyl	phenyl

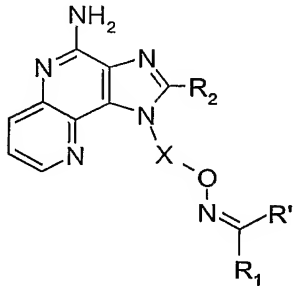
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Va, VIIa, VIIIb, and VIa) and the following R', R_1, X, and R_2 substituents, wherein each line of the table is matched with Formula Va, VIIa, VIIIb, or VIa to represent a specific embodiment of the invention.



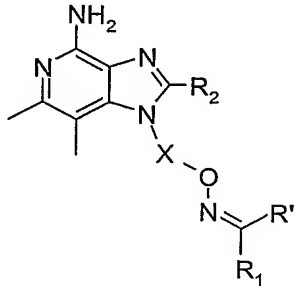
Va



VIIa



VIIIb



VIa

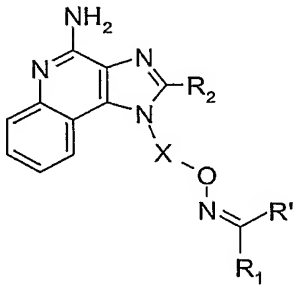
R_1	R'	X	R_2
hydrogen	hydrogen	$-(CH_2)_3-$	hydrogen
hydrogen	hydrogen	$-(CH_2)_3-$	ethyl
hydrogen	hydrogen	$-(CH_2)_3-$	propyl
hydrogen	hydrogen	$-(CH_2)_3-$	butyl
hydrogen	hydrogen	$-(CH_2)_3-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)_4-$	hydrogen
hydrogen	hydrogen	$-(CH_2)_4-$	ethyl
hydrogen	hydrogen	$-(CH_2)_4-$	propyl
hydrogen	hydrogen	$-(CH_2)_4-$	butyl
hydrogen	hydrogen	$-(CH_2)_4-$	ethoxymethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl
hydrogen	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl
hydrogen	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
hydrogen	methyl	$-(CH_2)_3-$	hydrogen
hydrogen	methyl	$-(CH_2)_3-$	ethyl
hydrogen	methyl	$-(CH_2)_3-$	propyl
hydrogen	methyl	$-(CH_2)_3-$	butyl
hydrogen	methyl	$-(CH_2)_3-$	ethoxymethyl
hydrogen	methyl	$-(CH_2)_4-$	hydrogen
hydrogen	methyl	$-(CH_2)_4-$	ethyl
hydrogen	methyl	$-(CH_2)_4-$	propyl
hydrogen	methyl	$-(CH_2)_4-$	butyl
hydrogen	methyl	$-(CH_2)_4-$	ethoxymethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl
hydrogen	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl
hydrogen	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	hydrogen
hydrogen	3-pyridyl	$-(CH_2)_3-$	ethyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	propyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	butyl
hydrogen	3-pyridyl	$-(CH_2)_3-$	ethoxymethyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	hydrogen

hydrogen	3-pyridyl	$-(CH_2)_4-$	ethyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	propyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	butyl
hydrogen	3-pyridyl	$-(CH_2)_4-$	ethoxymethyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	propyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	butyl
hydrogen	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	propyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	butyl
hydrogen	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
methyl	methyl	$-(CH_2)_3-$	hydrogen
methyl	methyl	$-(CH_2)_3-$	ethyl
methyl	methyl	$-(CH_2)_3-$	propyl
methyl	methyl	$-(CH_2)_3-$	butyl
methyl	methyl	$-(CH_2)_3-$	ethoxymethyl
methyl	methyl	$-(CH_2)_4-$	hydrogen
methyl	methyl	$-(CH_2)_4-$	ethyl
methyl	methyl	$-(CH_2)_4-$	propyl
methyl	methyl	$-(CH_2)_4-$	butyl
methyl	methyl	$-(CH_2)_4-$	ethoxymethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl
methyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl
methyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
methyl	3-pyridyl	$-(CH_2)_3-$	hydrogen
methyl	3-pyridyl	$-(CH_2)_3-$	ethyl
methyl	3-pyridyl	$-(CH_2)_3-$	propyl
methyl	3-pyridyl	$-(CH_2)_3-$	butyl
methyl	3-pyridyl	$-(CH_2)_3-$	ethoxymethyl
methyl	3-pyridyl	$-(CH_2)_4-$	hydrogen
methyl	3-pyridyl	$-(CH_2)_4-$	ethyl
methyl	3-pyridyl	$-(CH_2)_4-$	propyl
methyl	3-pyridyl	$-(CH_2)_4-$	butyl
methyl	3-pyridyl	$-(CH_2)_4-$	ethoxymethyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	propyl

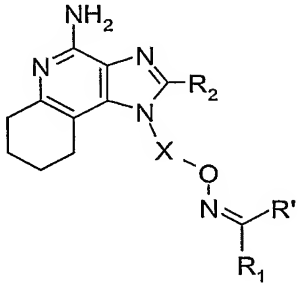
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	butyl
methyl	3-pyridyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	propyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	butyl
methyl	3-pyridyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
3-pyridyl	methyl	$-(CH_2)_3-$	hydrogen
3-pyridyl	methyl	$-(CH_2)_3-$	ethyl
3-pyridyl	methyl	$-(CH_2)_3-$	propyl
3-pyridyl	methyl	$-(CH_2)_3-$	butyl
3-pyridyl	methyl	$-(CH_2)_3-$	ethoxymethyl
3-pyridyl	methyl	$-(CH_2)_4-$	hydrogen
3-pyridyl	methyl	$-(CH_2)_4-$	ethyl
3-pyridyl	methyl	$-(CH_2)_4-$	propyl
3-pyridyl	methyl	$-(CH_2)_4-$	butyl
3-pyridyl	methyl	$-(CH_2)_4-$	ethoxymethyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	hydrogen
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	propyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	butyl
3-pyridyl	methyl	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	hydrogen
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	propyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	butyl
3-pyridyl	methyl	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	hydrogen
3-pyridyl	hydrogen	$-(CH_2)_3-$	ethyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	propyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	butyl
3-pyridyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	hydrogen
3-pyridyl	hydrogen	$-(CH_2)_4-$	ethyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	propyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	butyl
3-pyridyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl
3-pyridyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl
3-pyridyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl

methyl	hydrogen	$-(CH_2)_3-$	hydrogen
methyl	hydrogen	$-(CH_2)_3-$	ethyl
methyl	hydrogen	$-(CH_2)_3-$	propyl
methyl	hydrogen	$-(CH_2)_3-$	butyl
methyl	hydrogen	$-(CH_2)_3-$	ethoxymethyl
methyl	hydrogen	$-(CH_2)_4-$	hydrogen
methyl	hydrogen	$-(CH_2)_4-$	ethyl
methyl	hydrogen	$-(CH_2)_4-$	propyl
methyl	hydrogen	$-(CH_2)_4-$	butyl
methyl	hydrogen	$-(CH_2)_4-$	ethoxymethyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	hydrogen
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	propyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	butyl
methyl	hydrogen	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	hydrogen
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	propyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	butyl
methyl	hydrogen	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl

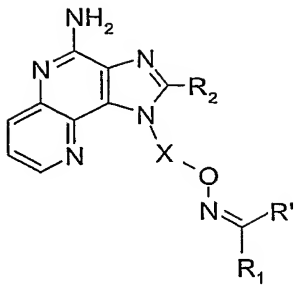
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (Va, VIIa, VIIIb, and VIa) and the following R', R_1, X, and R_2 substituents, wherein R' and R_1 join to form a ring, and each line of the table is matched with Formula Va, VIIa, VIIIb, or VIa to represent a specific embodiment of the invention.



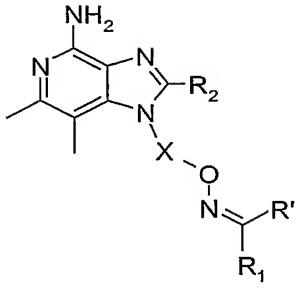
Va



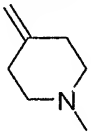
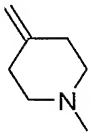
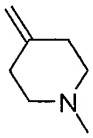
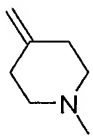
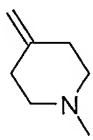
VIIa

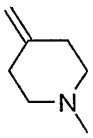
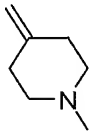
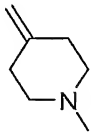
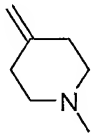
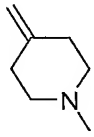
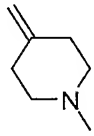
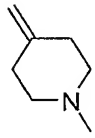
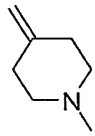


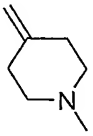
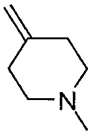
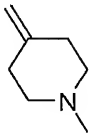
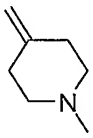
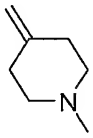
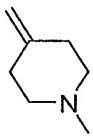
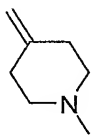
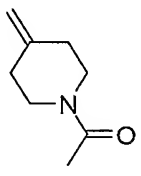
VIIIb

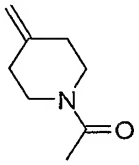
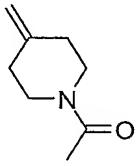
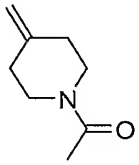
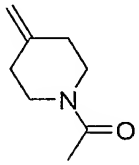
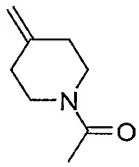
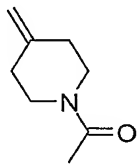
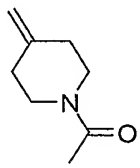


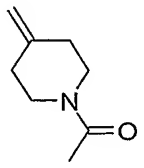
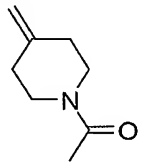
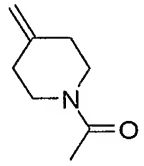
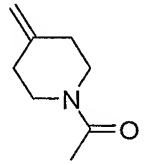
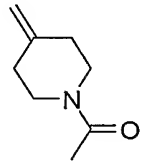
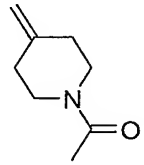
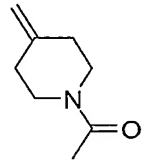
VIa

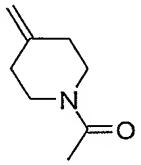
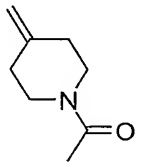
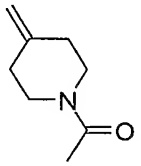
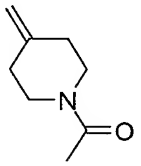
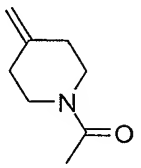
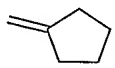
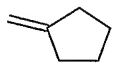
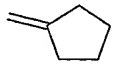
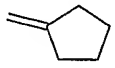
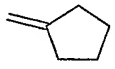
	X	R_2
	$-(CH_2)_3-$	hydrogen
	$-(CH_2)_3-$	ethyl
	$-(CH_2)_3-$	propyl
	$-(CH_2)_3-$	butyl
	$-(CH_2)_3-$	ethoxymethyl

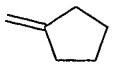
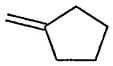
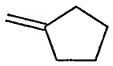
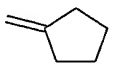
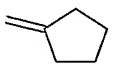
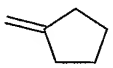
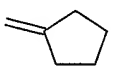
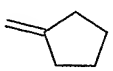
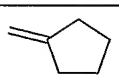
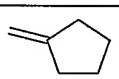
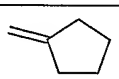
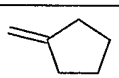
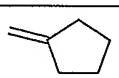
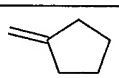
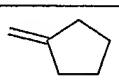
	$-(CH_2)_4-$	hydrogen
	$-(CH_2)_4-$	ethyl
	$-(CH_2)_4-$	propyl
	$-(CH_2)_4-$	butyl
	$-(CH_2)_4-$	ethoxymethyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen
	$-CH_2C(CH_3)_2CH_2-$	ethyl
	$-CH_2C(CH_3)_2CH_2-$	propyl

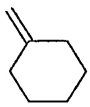
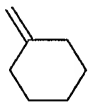
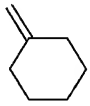
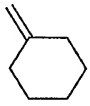
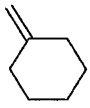
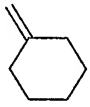
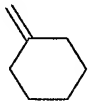
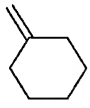
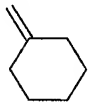
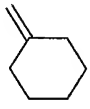
	$-CH_2C(CH_3)_2CH_2-$	butyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen
	$-(CH_2)_2O(CH_2)_2-$	ethyl
	$-(CH_2)_2O(CH_2)_2-$	propyl
	$-(CH_2)_2O(CH_2)_2-$	butyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
	$-(CH_2)_3-$	hydrogen

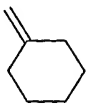
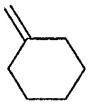
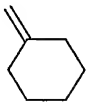
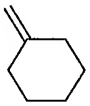
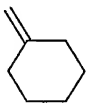
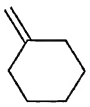
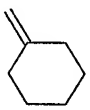
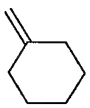
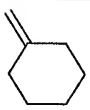
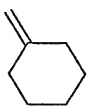
	$-(CH_2)_3-$	ethyl
	$-(CH_2)_3-$	propyl
	$-(CH_2)_3-$	butyl
	$-(CH_2)_3-$	ethoxymethyl
	$-(CH_2)_4-$	hydrogen
	$-(CH_2)_4-$	ethyl
	$-(CH_2)_4-$	propyl

	$-(CH_2)_4-$	butyl
	$-(CH_2)_4-$	ethoxymethyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen
	$-CH_2C(CH_3)_2CH_2-$	ethyl
	$-CH_2C(CH_3)_2CH_2-$	propyl
	$-CH_2C(CH_3)_2CH_2-$	butyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl

	$-(CH_2)_2O(CH_2)_2-$	hydrogen
	$-(CH_2)_2O(CH_2)_2-$	ethyl
	$-(CH_2)_2O(CH_2)_2-$	propyl
	$-(CH_2)_2O(CH_2)_2-$	butyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl
	$-(CH_2)_3-$	hydrogen
	$-(CH_2)_3-$	ethyl
	$-(CH_2)_3-$	propyl
	$-(CH_2)_3-$	butyl
	$-(CH_2)_3-$	ethoxymethyl

	$-(CH_2)_4-$	hydrogen
	$-(CH_2)_4-$	ethyl
	$-(CH_2)_4-$	propyl
	$-(CH_2)_4-$	butyl
	$-(CH_2)_4-$	ethoxymethyl
	$-CH_2C(CH_3)_2CH_2-$	hydrogen
	$-CH_2C(CH_3)_2CH_2-$	ethyl
	$-CH_2C(CH_3)_2CH_2-$	propyl
	$-CH_2C(CH_3)_2CH_2-$	butyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen
	$-(CH_2)_2O(CH_2)_2-$	ethyl
	$-(CH_2)_2O(CH_2)_2-$	propyl
	$-(CH_2)_2O(CH_2)_2-$	butyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl

	$-(CH_2)_3-$	hydrogen
	$-(CH_2)_3-$	ethyl
	$-(CH_2)_3-$	propyl
	$-(CH_2)_3-$	butyl
	$-(CH_2)_3-$	ethoxymethyl
	$-(CH_2)_4-$	hydrogen
	$-(CH_2)_4-$	ethyl
	$-(CH_2)_4-$	propyl
	$-(CH_2)_4-$	butyl
	$-(CH_2)_4-$	ethoxymethyl

	$-CH_2C(CH_3)_2CH_2-$	hydrogen
	$-CH_2C(CH_3)_2CH_2-$	ethyl
	$-CH_2C(CH_3)_2CH_2-$	propyl
	$-CH_2C(CH_3)_2CH_2-$	butyl
	$-CH_2C(CH_3)_2CH_2-$	ethoxymethyl
	$-(CH_2)_2O(CH_2)_2-$	hydrogen
	$-(CH_2)_2O(CH_2)_2-$	ethyl
	$-(CH_2)_2O(CH_2)_2-$	propyl
	$-(CH_2)_2O(CH_2)_2-$	butyl
	$-(CH_2)_2O(CH_2)_2-$	ethoxymethyl

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to induce cytokine biosynthesis when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 micromolar (μM).

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test

compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at -30°C to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set

forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

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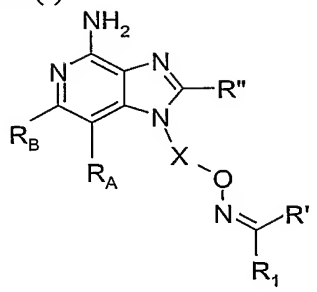
WHAT IS CLAIMED IS:

1. A compound of formula (I)



I

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

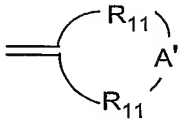
haloalkyl,

hydroxyalkyl,

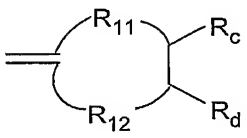
alkoxy,

dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,
halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxyl,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or

R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_6 is independently selected from the group consisting of =O and =S;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R" is hydrogen or a non-interfering substituent; and

each R'" is a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

2. The compound or salt of claim 1 wherein X is -CH(R_{9a})-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups.

3. The compound or salt of claim 2 wherein X is -C_{3-5} alkylene- or -$CH_2CH_2OCH_2CH_2$-.

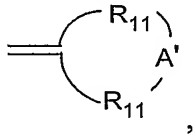
4. The compound or salt of any one of claims 1 through 3 wherein at least one of R' or R_1 is hydrogen.

5. The compound or salt of any one of claims 1 through 3 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

6. The compound or salt of claim 5 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

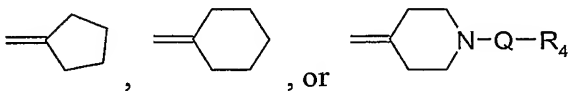
7. The compound or salt of claim 5 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

8. The compound or salt of any one of claims 1 through 3 wherein R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl.

9. The compound or salt of claim 8 wherein the ring system is



, , or .

10. The compound or salt of any one of claims 1 through 3 wherein R_1 and R' are each methyl.

11. The compound or salt of any one of claims 1 through 10 wherein:

R" is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

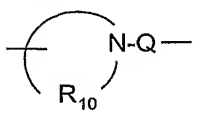
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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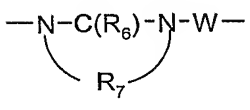

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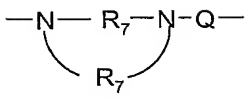
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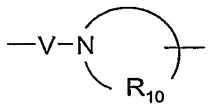
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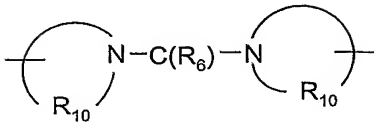
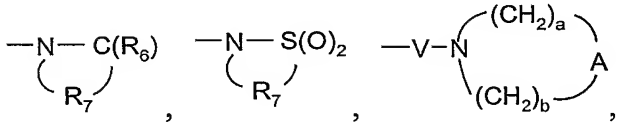

;

R_5 is selected from the group consisting of: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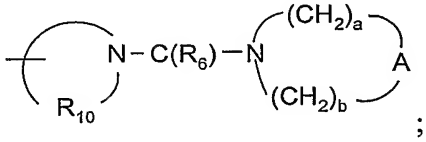

and ;

each R_7 is independently C_{2-7} alkylene;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

12. The compound or salt of any one of claims 1 through 10 wherein R" is hydrogen, alkoxyalkylenyl, $-R_4$, $-X'-R_4$, or $-X'-Y-R_4$; wherein X' is C_{1-2} alkylene; Y is $-S(O)_{0-2}-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-$, $-C(R_6)-O-$, $-O-C(R_6)-$, $-O-C(O)-O-$, $-N(R_8)-Q-$, $-C(R_6)-N(R_8)-$, $-O-C(R_6)-N(R_8)-$, or $-C(R_6)-N(OR_9)-$; and R_4 is alkyl.

13. The compound or salt of claim 12 wherein R" is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

14. The compound or salt of claim 13 wherein R" is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

15. The compound or salt of any one of claims 1 through 10 wherein R" is selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and

-C(O)-heteroaryl;

wherein:

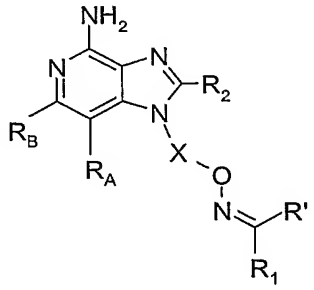
Y" is –O– or –S(O)$_{0-2}$-; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

16. The compound or salt of any one of claims 1 through 15 wherein R_A and R_B form a fused aryl ring or heteroaryl ring containing one N, wherein the aryl ring or heteroaryl ring is unsubstituted.

17. The compound or salt of any one of claims 1 through 15 wherein R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one N, wherein the saturated ring is unsubstituted.

18. A compound of the formula (II):



II

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

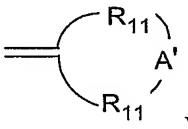
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,

-N(R_8)-C(O)-alkyl,

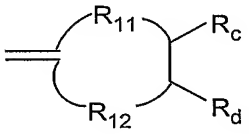
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxyl,

alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_2 is selected from the group consisting of:
$-R_4$,
$-X'-R_4$,
$-X'-Y-R_4$, and
$-X'-R_5$;

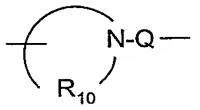
R_3 is selected from the group consisting of:
$-Z-R_4$,
$-Z-X'-R_4$,
$-Z-X'-Y-R_4$, and
$-Z-X'-R_5$;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:
$-S(O)_{0-2}-$,
$-S(O)_2-N(R_8)-$,
$-C(R_6)-$,
$-C(R_6)-O-$,
$-O-C(R_6)-$,
$-O-C(O)-O-$,
$-N(R_8)-Q-$,
$-C(R_6)-N(R_8)-$,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,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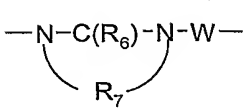
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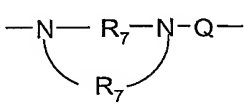
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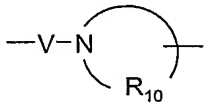
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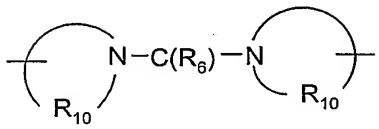
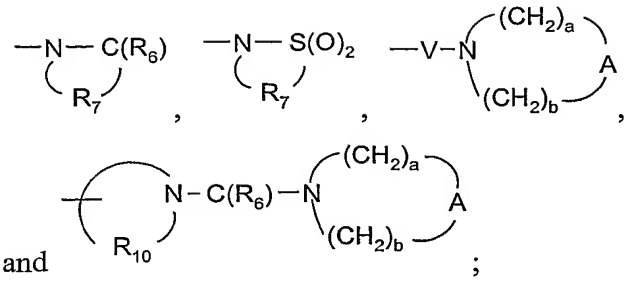

;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:



and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and

$-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

19. The compound or salt of claim 18 wherein X is $-CH(R_{9a})$-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups.

20. The compound or salt of claim 19 wherein X is $-C_{3-5}$ alkylene- or $-CH_2CH_2OCH_2CH_2-$.

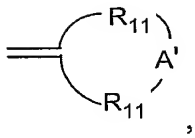
21. The compound or salt of any one of claims 18 through 20 wherein at least one of R' or R_1 is hydrogen.

22. The compound or salt of any one of claims 18 through 20 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

23. The compound or salt of claim 22 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

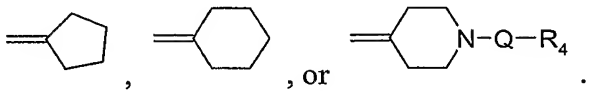
24. The compound or salt of claim 22 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

25. The compound or salt of any one of claims 18 through 20 wherein R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl.

26. The compound or salt of claim 25 wherein the ring system is



27. The compound or salt of any one of claims 18 through 20 wherein R_1 and R' are each methyl.

28. The compound or salt of any one of claims 18 through 27 wherein R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X'-R_4, or -X'-Y-R_4; wherein X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, or -$C(R_6)$-$N(OR_9)$-; and R_4 is alkyl.

29. The compound or salt of claim 28 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

30. The compound or salt of claim 29 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

31. The compound or salt of any one of claims 18 through 27 wherein R_2 is selected from the group consisting of:

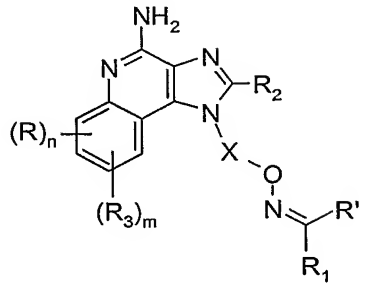
hydrogen,
alkyl,
alkenyl,
aryl,

heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;
wherein:
Y" is –O– or $-S(O)_{0-2}-$; and
each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

32. The compound or salt of any one of claims 18 through 31 wherein R_A and R_B form a fused aryl ring or heteroaryl ring containing one N, wherein the aryl ring or heteroaryl ring is unsubstituted.

33. The compound or salt of any one of claims 18 through 31 wherein R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one N, wherein the saturated ring is unsubstituted.

34. A compound of the formula (III):



III

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

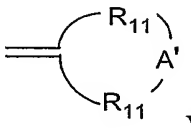
$-C(O)-N(R_8)_2$,

$-N(R_8)$-C(O)-alkyl,

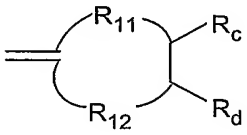
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$, and

$-Z-X'-R_5$;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

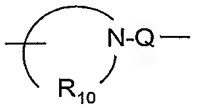
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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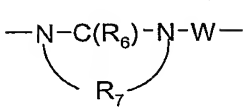

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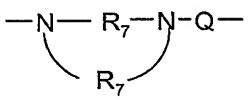

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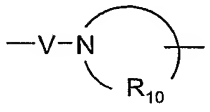
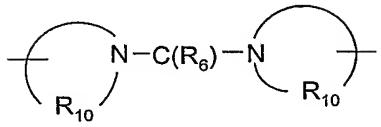


, and



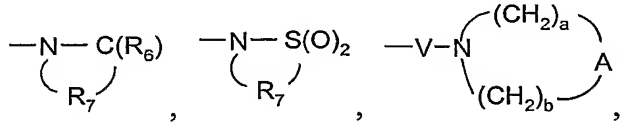
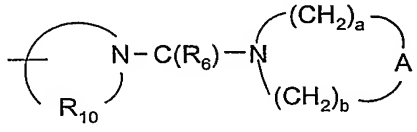
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino,

dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:

and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and

$-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

n is an integer from 0 to 4; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

35. The compound or salt of claim 34 wherein X is $-CH(R_{9a})$-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups.

36. The compound or salt of claim 35 wherein X is $-C_{3-5}$ alkylene- or $-CH_2CH_2OCH_2CH_2-$.

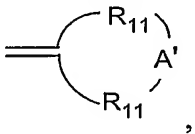
37. The compound or salt of any one of claims 34 through 36 wherein at least one of R' or R_1 is hydrogen.

38. The compound or salt of any one of claims 34 through 36 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

39. The compound or salt of claim 38 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

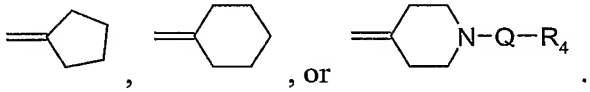
40. The compound or salt of claim 38 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

41. The compound or salt of any one of claims 34 through 36 wherein R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl.

42. The compound or salt of claim 41 wherein the ring system is



, , or .

43. The compound or salt of any one of claims 34 through 36 wherein R_1 and R' are each methyl.

44. The compound or salt of any one of claims 34 through 43 wherein R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X'-R_4, or -X'-Y-R_4; wherein X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-; and R_4 is alkyl.

45. The compound or salt of claim 44 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

46. The compound or salt of claim 45 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

47. The compound or salt of any one of claims 34 through 43 wherein R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y"-alkyl,

alkylene-Y"-alkenyl,

alkylene-Y"-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

halogen,

$-N(R_{8a})_2$,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

wherein:

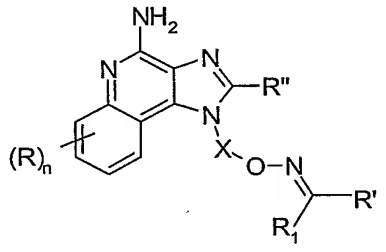
Y" is –O– or $-S(O)_{0-2}-$; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

48. The compound or salt of any one of claims 34 through 47 wherein m and n are each 0.

49. The compound or salt of any one of claims 34 through 47 wherein m is 1, and R_3 is phenyl, pyridin-3-yl, pyridin-4-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-ethoxyphenyl, 3-(morpholine-4-carbonyl)phenyl, or 3-(*N,N*-dimethylaminocarbonyl)phenyl.

50. A compound of the formula (IV):



IV

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

alkylene-aryl,

heteroaryl,

heterocyclyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,
haloalkyl,
hydroxyalkyl,
-O-alkyl,
-S-alkyl,
-O-haloalkyl,
halogen,
nitrile,
aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is an integer from 0 to 4;

each R and R" are independently selected from the group consisting of hydrogen and non-interfering substituents;

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl;

or a pharmaceutically acceptable salt thereof.

51. The compound or salt of claim 50 wherein X is -CH(R_{9a})-C_{1-5}alkylene-.

52. The compound or salt of claim 51 wherein X is propylene or butylene.

53. The compound or salt of any one of claims 50 through 52 wherein at least one of R' or R_1 is hydrogen.

54. The compound or salt of any one of claims 50 through 52 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

55. The compound or salt of claim 54 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

56. The compound or salt of claim 54 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

57. The compound or salt of any one of claims 50 through 52 wherein R_1 and R' join together to form a ring system.

58. The compound or salt of claim 57 wherein the ring system is optionally substituted by one or more substituents selected from the group consisting of alkyl, aryl, alkylene-aryl, and -C(O)-alkyl.

59. The compound or salt of any one of claims 50 through 58 wherein each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl.

60. The compound or salt of any one of claims 50 through 58 wherein n is 0.

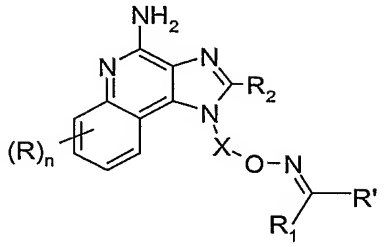
61. The compound or salt of any one of claims 50 through 60 wherein R" is selected from the group consisting of:

hydrogen,

alkyl,
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;
wherein:
Y" is –O– or $–S(O)_{0-2}$-; and
each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

62. The compound or salt of claim 61 wherein R" is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

63. A compound of the formula (V):



V

wherein:

X is selected from the group consisting of –CH(R_{9a})-alkylene- and –CH(R_{9a})-alkenylene-;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

alkylene-aryl,

heteroaryl,

heterocyclyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

-O-alkyl,

-S-alkyl,

-O-haloalkyl,

halogen,

nitrile,

aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

n is an integer from 0 to 4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

R_2 is selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,
halogen,
-N(R_{8a})$_2$,
-C(O)-C_{1-10} alkyl,
-C(O)-O-C_{1-10} alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

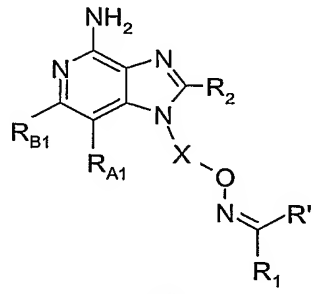
Y" is –O– or $–S(O)_{0-2}$-;

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl;

or a pharmaceutically acceptable salt thereof.

64. A compound of the formula (VI):



VI

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

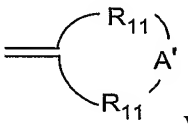
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

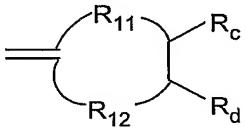
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)-C(O)$-alkyl,
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

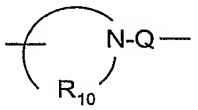
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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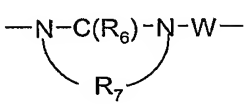

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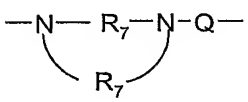

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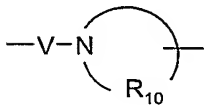

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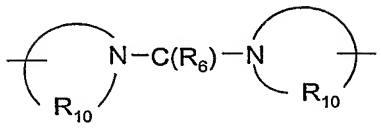
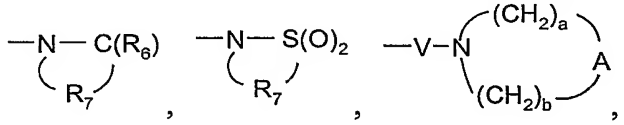


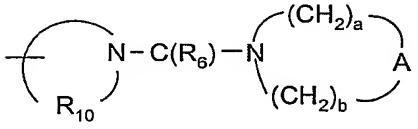
;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen,

nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:





and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and

$-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

65. The compound or salt of claim 64 wherein X is $-CH(R_{9a})$-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups.

66. The compound or salt of claim 65 wherein X is $-C_{3-5}$ alkylene- or $-CH_2CH_2OCH_2CH_2-$.

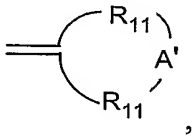
67. The compound or salt of any one of claims 64 through 66 wherein at least one of R' or R_1 is hydrogen.

68. The compound or salt of any one of claims 64 through 66 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

69. The compound or salt of claim 68 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

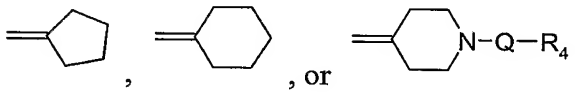
70. The compound or salt of claim 68 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

71. The compound or salt of any one of claims 64 through 66 wherein R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl.

72. The compound or salt of claim 71 wherein the ring system is



, , or .

73. The compound or salt of any one of claims 64 through 66 wherein R_1 and R' are each methyl.

74. The compound or salt of any one of claims 64 through 73 wherein R_2 is hydrogen, alkoxyalkylenyl -R_4, -X'-R_4, or -X'-Y-R_4; wherein X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-; and R_4 is alkyl.

75. The compound or salt of claim 74 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

76. The compound or salt of claim 75 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

77. The compound or salt of any one of claims 64 through 73 wherein R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

heteroaryl,

heterocyclyl,

alkylene-Y"-alkyl,

alkylene-Y"-alkenyl,

alkylene-Y"-aryl, and

alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

hydroxyl,

halogen,

$-N(R_{8a})_2$,

$-C(O)-C_{1-10}$ alkyl,

$-C(O)-O-C_{1-10}$ alkyl,

$-N_3$,

aryl,

heteroaryl,

heterocyclyl,

-C(O)-aryl, and

-C(O)-heteroaryl;

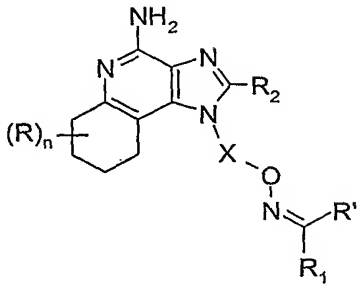
wherein:

Y" is –O– or $–S(O)_{0-2}$-; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

78. The compound or salt of any one of claims 64 through 77 wherein R_{A1} and R_{B1} are each methyl.

79. A compound of the formula (VII):



VII

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

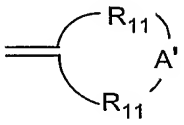
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

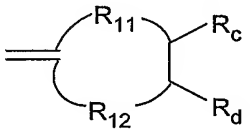
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-$N(R_8)_2$,
-$N(R_8)$-C(O)-alkyl,
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

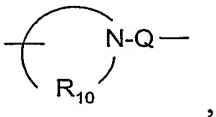
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

-C(R_6)-N(OR_9)-,



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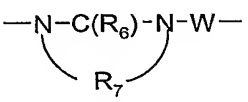

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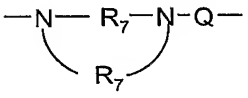

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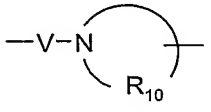
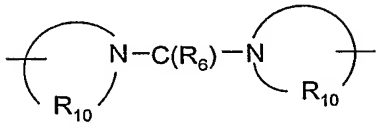


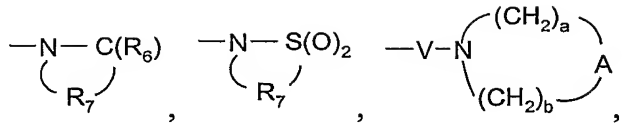
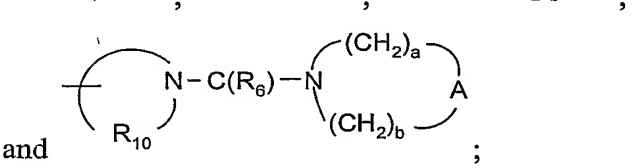
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and

-$C(R_6)$-$N(OR_9)$-;

V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

each W is independently selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; and

n is an integer from 0 to 4;

or a pharmaceutically acceptable salt thereof.

80. The compound or salt of claim 79 wherein X is -$CH(R_{9a})$-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups.

81. The compound or salt of claim 80 wherein X is -C_{3-5} alkylene- or -$CH_2CH_2OCH_2CH_2$-.

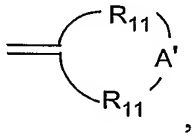
82. The compound or salt of any one of claims 79 through 81 wherein at least one of R' or R_1 is hydrogen.

83. The compound or salt of any one of claims 79 through 81 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

84. The compound or salt of claim 83 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

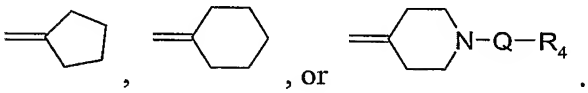
85. The compound or salt of claim 83 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

86. The compound or salt of any one of claims 79 through 81 wherein R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl.

87. The compound or salt of claim 86 wherein the ring system is



88. The compound or salt of any one of claims 79 through 81 wherein R_1 and R' are each methyl.

89. The compound or salt of any one of claims 79 through 88 wherein R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X'-R_4, or -X'-Y-R_4; wherein X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-, -$C(R_6)$-O-, -O-$C(R_6)$-, -O-C(O)-O-, -$N(R_8)$-Q-, -$C(R_6)$-$N(R_8)$-, -O-$C(R_6)$-$N(R_8)$-, or -$C(R_6)$-$N(OR_9)$-; and R_4 is alkyl.

90. The compound or salt of claim 89 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

91. The compound or salt of claim 90 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

92. The compound or salt of any one of claims 79 through 88 wherein R_2 is selected from the group consisting of:

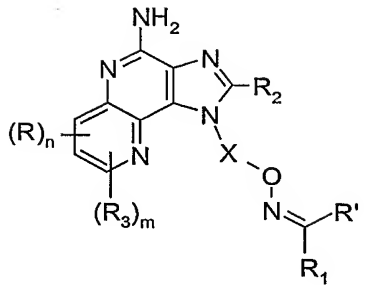
hydrogen,

alkyl,

alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;
wherein:
Y" is –O– or $–S(O)_{0-2}$-; and
each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

93. The compound or salt of any one of claims 79 through 92 wherein n is 0.

94. A compound of the formula (VIII):



VIII

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

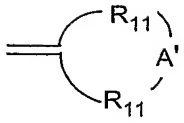
heterocyclyl,

heterocyclylalkylenyl, and

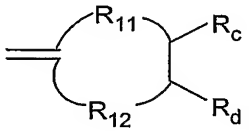
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)-C(O)$-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$, and

$-Z-X'-R_5$;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

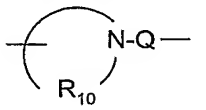
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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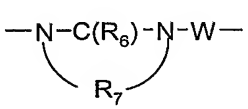

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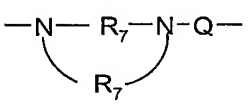

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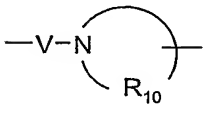
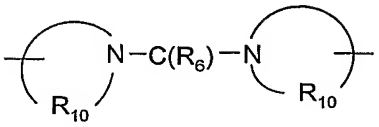


, and

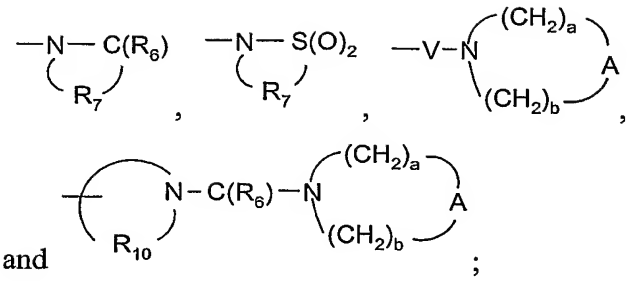


;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:



and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and

$-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

n is an integer from 0 to 3; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

95. The compound or salt of claim 94 wherein X is $-CH(R_{9a})$-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups.

96. The compound or salt of claim 95 wherein X is $-C_{3-5}$ alkylene- or $-CH_2CH_2OCH_2CH_2-$.

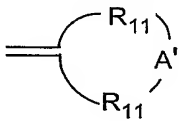
97. The compound or salt of any one of claims 94 through 96 wherein at least one of R' or R_1 is hydrogen.

98. The compound or salt of any one of claims 94 through 96 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

99. The compound or salt of claim 98 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

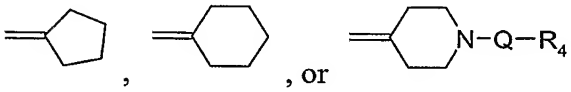
100. The compound or salt of claim 98 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

101. The compound or salt of any one of claims 94 through 96 wherein R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl.

102. The compound or salt of claim 101 wherein the ring system is



, , or .

103. The compound or salt of any one of claim 94 through 96 wherein R_1 and R' are each methyl.

104. The compound or salt of any one of claims 94 through 103 wherein R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X'-R_4, or -X'-Y-R_4; wherein X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-; and R_4 is alkyl.

105. The compound or salt of claim 104 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

106. The compound or salt of claim 105 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

107. The compound or salt of any one of claims 94 through 103 wherein R_2 is selected from the group consisting of:

hydrogen,

alkyl,

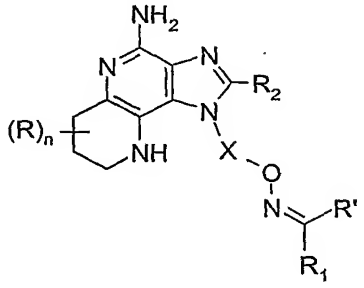
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;
wherein:
Y" is –O– or $–S(O)_{0-2}$-; and
each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

108. The compound or salt of any one of claims 94 through 107 wherein m and n are each 0.

109. The compound or salt of any one of claims 94 through 107 wherein m is 1, and R_3 is phenyl, pyridin-3-yl, pyridin-4-yl, 5-(hydroxymethyl)pyridin-3-yl, 2-

ethoxyphenyl, 3-(morpholine-4-carbonyl)phenyl, or 3-(*N,N*-dimethylaminocarbonyl)phenyl.

110. A compound of the formula (IX):



IX

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

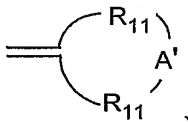
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

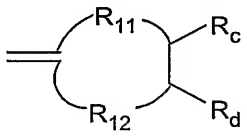
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-$C(O)$-$N(R_8)_2$,
-$N(R_8)$-C(O)-alkyl,
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

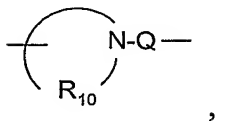
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

-C(R_6)-N(OR_9)-,



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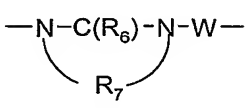

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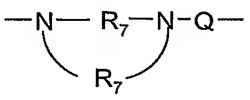

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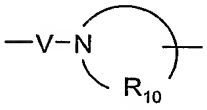
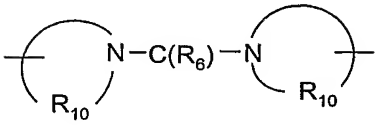


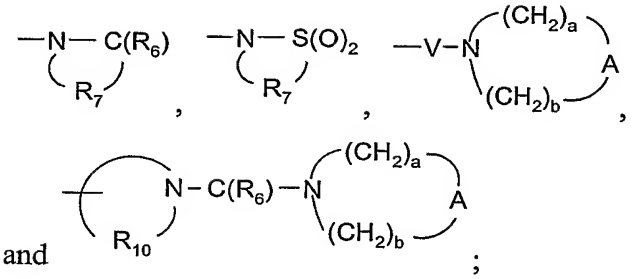
, and



;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and

$-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7; and

n is an integer from 0 to 3;

or a pharmaceutically acceptable salt thereof.

111. The compound or salt of claim 110 wherein X is $-CH(R_{9a})$-alkylene-, wherein the alkylene is optionally interrupted by one or more -O- groups.

112. The compound or salt of claim 111 wherein X is $-C_{3-5}$ alkylene- or $-CH_2CH_2OCH_2CH_2-$.

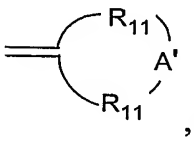
113. The compound or salt of any one of claims 110 through 112 wherein at least one of R' or R_1 is hydrogen.

114. The compound or salt of any one of claims 110 through 112 wherein at least one of R' or R_1 is selected from the group consisting of aryl, heteroaryl, and alkyl, wherein the aryl, heteroaryl, and alkyl are optionally substituted.

115. The compound or salt of claim 114 wherein at least one of R' or R_1 is aryl or substituted aryl and at least one of R' or R_1 is hydrogen.

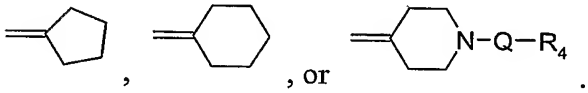
116. The compound or salt of claim 114 wherein at least one of R' or R_1 is heteroaryl or substituted heteroaryl and at least one of R' or R_1 is hydrogen.

117. The compound or salt of any one of claims 110 through 112 wherein R_1 and R' join together to form a ring system of the formula



, wherein A' is -N(-Q-R_4)- or -CH_2-, Q is a bond or -C(O)-, and R_4 is alkyl.

118. The compound or salt of claim 117 wherein the ring system is



, , or .

119. The compound or salt of any one of claims 110 through 112 wherein R_1 and R' are each methyl.

120. The compound or salt of any one of claims 110 through 119 wherein R_2 is hydrogen, alkoxyalkylenyl, -R_4, -X'-R_4, or -X'-Y-R_4; wherein X' is C_{1-2} alkylene; Y is -$S(O)_{0-2}$-, -$S(O)_2$-N(R_8)-, -C(R_6)-, -C(R_6)-O-, -O-C(R_6)-, -O-C(O)-O-, -N(R_8)-Q-, -C(R_6)-N(R_8)-, -O-C(R_6)-N(R_8)-, or -C(R_6)-N(OR_9)-; and R_4 is alkyl.

121. The compound or salt of claim 120 wherein R_2 is selected from the group consisting of hydrogen, alkyl, and alkoxyalkylenyl.

122. The compound or salt of claim 121 wherein R_2 is selected from the group consisting of hydrogen, methyl, ethyl, propyl, butyl, ethoxymethyl, 2-methoxyethyl, and methoxymethyl.

123. The compound or salt of any one of claims 110 through 119 wherein R_2 is selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

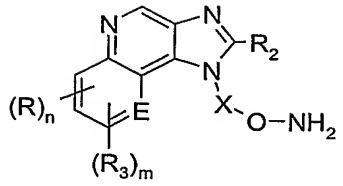
wherein:

Y" is –O– or $–S(O)_{0-2}$-; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl.

124. The compound or salt of any one of claims 110 through 123 wherein n is 0.

125. A compound of the formula (X):



X

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and n is 0 or 1, and with the further proviso that when E is CR and m is 1, n is 0;

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

n is an integer from 0 to 3;

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

-Z-X'-R_4,

-Z-X'-Y-R_4, and

-Z-X'-R_5;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

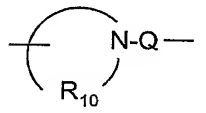
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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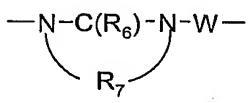

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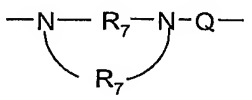

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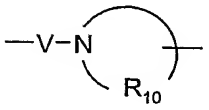
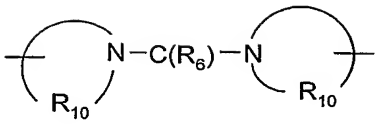


, and

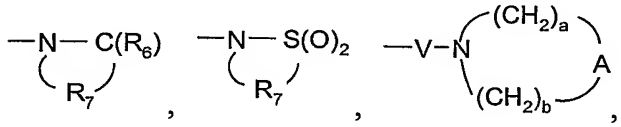


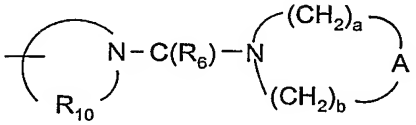
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:



and 

;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

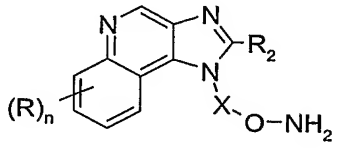
each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

or a pharmaceutically acceptable salt thereof.

126. A compound of the formula (XI):



XI

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

n is an integer from 0 to 4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

R_2 is selected from the group consisting of:

hydrogen,

alkyl,
alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

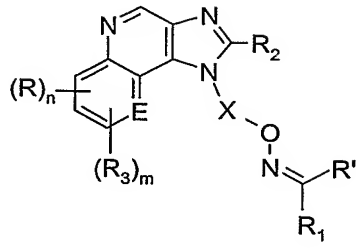
Y" is –O– or $–S(O)_{0-2}$-;

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl; and

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

or a pharmaceutically acceptable salt thereof.

127. A compound of the formula (XII):



XII

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and n is 0 or 1, and with the further proviso that when E is CR and m is 1, n is 0;

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,

hydroxyl,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

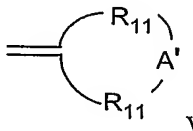
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

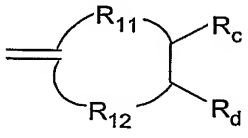
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
nitrile,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-$N(R_8)_2$,
-$N(R_8)$-C(O)-alkyl,
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4, and

-X'-R_5;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4, and

-Z-X'-R_5;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-C(R_6)-,

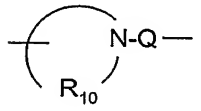
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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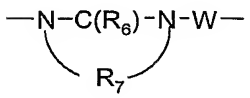

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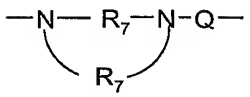

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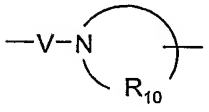

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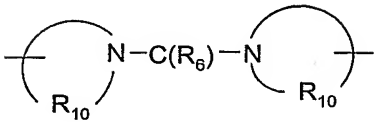


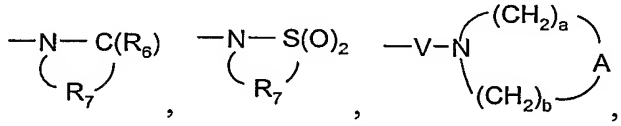
;

Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino,

dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of: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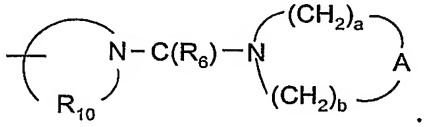

and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and

$-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$;

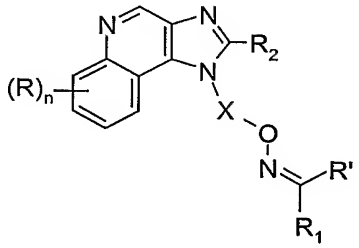
a and b are independently integers from 1 to 6 with the proviso that a + b is $\leq$ 7;

n is an integer from 0 to 3; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

128. A compound of the formula (XIII):



XIII

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

n is an integer from 0 to 4;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,
alkenyl,
aryl,
alkylene-aryl,
heteroaryl,
heterocyclyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
-O-alkyl,
-S-alkyl,
-O-haloalkyl,
halogen,
nitrile,
aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

R_2 is selected from the group consisting of:
hydrogen,
alkyl,

alkenyl,
aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl;

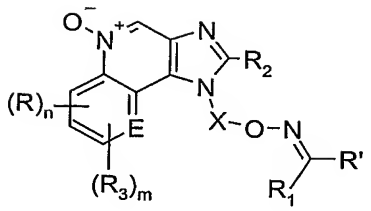
Y" is –O– or $–S(O)_{0-2}$-;

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl; and

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

or a pharmaceutically acceptable salt thereof.

129. A compound of the formula (XIV):



XIV

wherein:

E is selected from the group consisting of CH, CR, CR_3, and N, with the proviso that when E is CR_3, m is 0, and n is 0 or 1, and with the further proviso that when E is CR and m is 1, n is 0;

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

each R is independently selected from the group consisting of:

halogen,
hydroxyl,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-$S(O)_2$-alkyl,

-NH-$S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

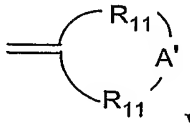
-$C(O)$-$N(R_8)_2$,

-$N(R_8)$-C(O)-alkyl,

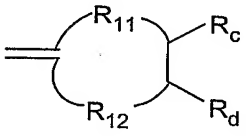
-O-C(O)-alkyl, and

-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$, and

$-X'-R_5$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$, and

$-Z-X'-R_5$;

each X' is independently selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

each Y is independently selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

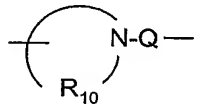
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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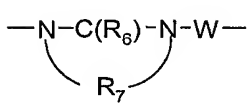

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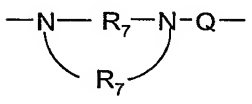

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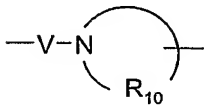
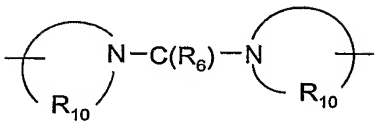


, and



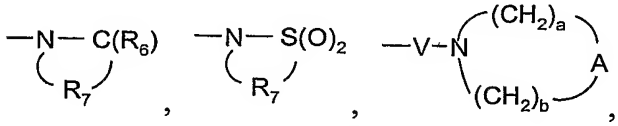
;

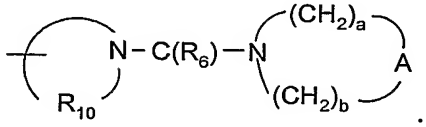
Z is a bond or -O-;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino,

dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

each R_5 is independently selected from the group consisting of:





;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

each A is independently selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and

$-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

each V is independently selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$;

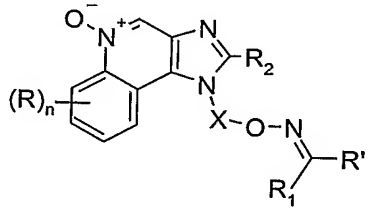
a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

n is an integer from 0 to 3; and

m is 0 or 1, with the proviso that when m is 1, n is 0 or 1;

or a pharmaceutically acceptable salt thereof.

130. A compound of the formula (XV):



XV

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-;

each R is independently selected from the group consisting of alkyl, alkoxy, halogen, hydroxyl, and trifluoromethyl;

n is an integer from 0 to 4;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,
aryl,
alkylene-aryl,
heteroaryl,
heterocyclyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl or heterocyclyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
alkyl,
haloalkyl,
hydroxyalkyl,
-O-alkyl,
-S-alkyl,
-O-haloalkyl,
halogen,
nitrile,
aryl,
heteroaryl,
heterocyclyl,
-O-aryl,
-O-alkylene-aryl,
-C(O)-O-alkyl,
-C(O)-N(R_{8a})$_2$, and
-N(R_{8a})-C(O)-alkyl;

or R_1 and R' can join together to form a ring system containing one or two saturated or unsaturated rings optionally including one or more heteroatoms;

R_2 is selected from the group consisting of:
hydrogen,
alkyl,
alkenyl,

aryl,
heteroaryl,
heterocyclyl,
alkylene-Y"-alkyl,
alkylene-Y"-alkenyl,
alkylene-Y"-aryl, and
alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
hydroxyl,
halogen,
$-N(R_{8a})_2$,
$-C(O)-C_{1-10}$ alkyl,
$-C(O)-O-C_{1-10}$ alkyl,
$-N_3$,
aryl,
heteroaryl,
heterocyclyl,
-C(O)-aryl, and
-C(O)-heteroaryl,

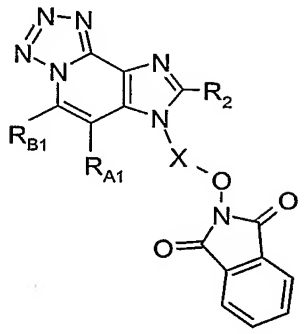
Y" is –O– or $–S(O)_{0-2}$-;

R_{9a} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups; and

each R_{8a} is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, and C_{2-10} alkenyl;

or a pharmaceutically acceptable salt thereof.

131. A compound of the formula (XVI):



XVI

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_2 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4, and

-X'-R_5;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene,

heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

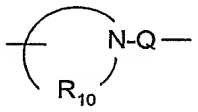
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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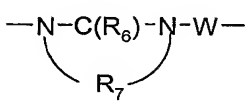

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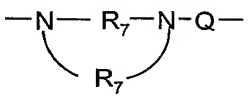

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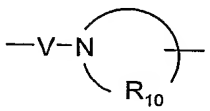

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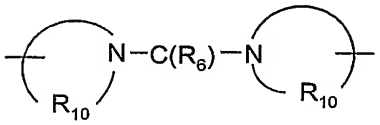
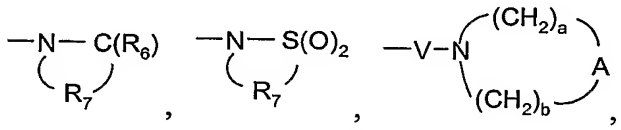


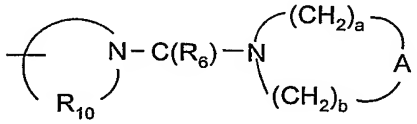
;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl,

heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:





;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

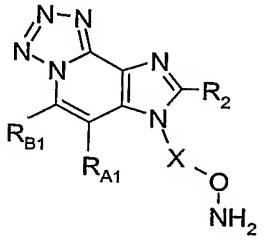
W is selected from the group consisting of a bond,

-C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

a pharmaceutically acceptable salt thereof.

132. A compound of the formula (XVII):



XVII

wherein:

X is selected from the group consisting of -CH(R_{9a})-alkylene- and -CH(R_{9a})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_2 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4, and

-X'-R_5;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

-$N(R_9)_2$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

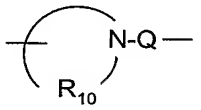
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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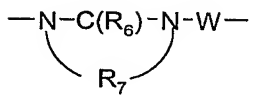

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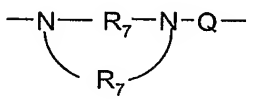

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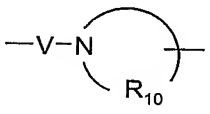

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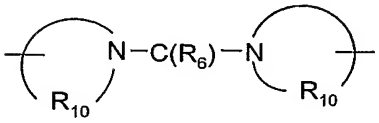
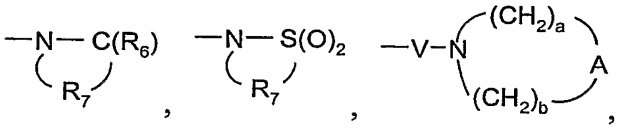
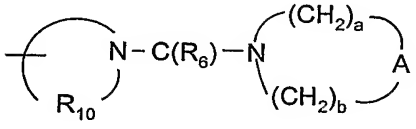


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



and  ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$,

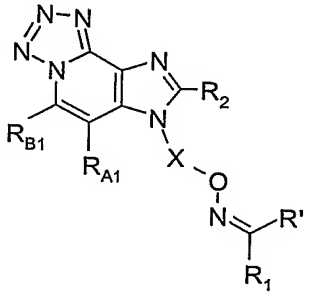
$-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

133. A compound of the formula (XVIII):



XVIII

wherein:

X is selected from the group consisting of $-CH(R_{9a})$-alkylene- and $-CH(R_{9a})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 and R' are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxyl,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

nitrile,

nitro,

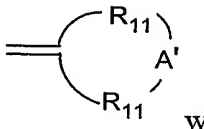
aryl,

heteroaryl,

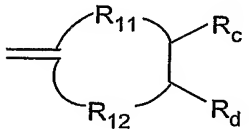
heterocyclyl,

aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-C(O)-alkyl, and
-C(O)-alkyl;

or R_1 and R' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_2 is selected from the group consisting of:

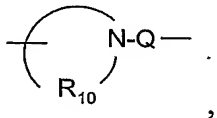
-R_4,
-X'-R_4,
-X'-Y-R_4, and
-X'-R_5;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene, wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated with arylene, heteroarylene, or heterocyclylene, and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-S(O)$_{0-2}$-,
-S(O)$_2$-N(R_8)-,
-C(R_6)-,

-C(R_6)-O-,
-O-C(R_6)-,
-O-C(O)-O-,
-N(R_8)-Q-,
-C(R_6)-N(R_8)-,
-O-C(R_6)-N(R_8)-,
-C(R_6)-N(OR_9)-,



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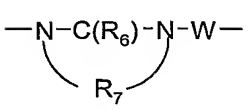

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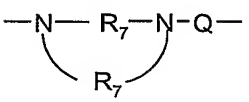

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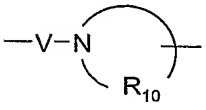
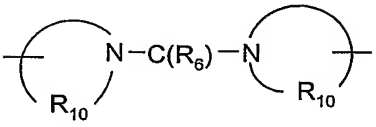


, and

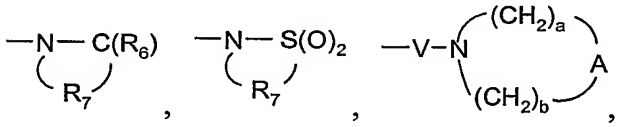


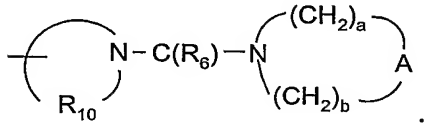
;

each R_4 is independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl, wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxyl, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino,

dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:





and ;

each R_6 is independently selected from the group consisting of =O and =S;

each R_7 is independently C_{2-7} alkylene;

each R_8 is independently selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

each R_9 is independently selected from the group consisting of hydrogen and alkyl;

R_{9a} is selected from the group consisting of hydrogen and alkyl which is optionally interrupted by one or more -O- groups;

each R_{10} is independently C_{3-8} alkylene;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxyl, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

each R_{11} is independently C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

A is selected from the group consisting of -O-, -C(O)-, $-CH_2-$, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and

$-CH_2-$;

each Q is independently selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

each W is independently selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$; or a pharmaceutically acceptable salt thereof.

134. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 124 in combination with a pharmaceutically acceptable carrier.

135. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 124 to the animal.

136. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 124 to the animal.

137. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 124 to the animal.